ORIGINAL ARTICLE

Changes in Driving Pressure vs Oxygenation as Predictor of Mortality in Moderate to Severe Acute Respiratory Distress Syndrome Patients Receiving Prone Position Ventilation

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Abstract

Background: Prone position ventilation (PPV) causes improvement in oxygenation, nevertheless, mortality in severe acute respiratory distress syndrome (ARDS) remains high. The changes in the driving pressure (DP) and its role in predicting mortality in moderate to severe ARDS patients receiving PPV is unexplored.

Methods: A prospective observational study, conducted between September 2020 and February 2023 on moderate-severe ARDS patients requiring PPV. The values of DP and oxygenation (ratio of partial pressure of arterial oxygen to fraction of inspired oxygen [PaO_2/FiO_2]) before, during, and after PPV were recorded. The aim was to compare the DP and oxygenation before, during and after PPV sessions among moderate-severe ARDS patients, and determine the best predictor of mortality.

Results: Total of 52 patients were included; 28-day mortality was 57%. Among the survivors, DP prior to PPV as compared to post-PPV session reduced significantly, from 16.36 ± 2.57 cmH_2O to 13.91 ± 1.74 cmH_2O (*p*-value < 0.001), whereas DP did not reduce in the non-survivors (19.43 ± 3.16 to 19.70 ± 3.15 cmH_2O (*p*-value = 0.318)]. Significant improvement in PaO_2/FiO_2 before PPV to post-PPV among both the survivors [92.75 [67.5–117.75]) to [205.50 (116.25–244.50)], (*p*-value < 0.001) and also among the non-survivors [87.90 (67.75–100.75)] to [112 (88.00–146.50)], (*p*-value < 0.001) was noted. Logistic regression analysis showed DP after PPV session as best predictor of mortality (*p*-value = 0.044) and its AUROC to predict mortality was 0.939, cut-off ≥16 cmH_2O, 90% sensitivity, 82% specificity. The Kaplan–Meier curve of DP after PPV ≥16 cmH_2O and <16 cmH_2O was significant (Log-rank Mantel-Cox *p*-value < 0.001).

Conclusion: Prone position ventilation-induced decrease in DP is prognostic marker of survival than the increase in PaO_2/FiO_2. There is a primacy of DP, rather than oxygenation, in predicting mortality in moderate-severe ARDS. Post-PPV session DP ≥16 cmH_2O was an independent predictor of mortality.

Keywords: Acute respiratory distress syndrome, Driving pressure, Mortality, Prone position ventilation.

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Highlights

This study showed that even a significant improvement in PaO_2/FiO_2 after PPV in moderate-severe ARDS patients, is not translated to a reduction in mortality. The DP remaining high at ≥16 cmH_2O after sessions of PPV is a reliable predictor of mortality. The significant reduction of DP after PPV in moderate-severe ARDS patients discriminates the survivors from non-survivors, whereas the significant improvement in oxygenation cannot.

Introduction

Prone position ventilation (PPV) has led to an improvement in oxygenation in seven randomized controlled trials (RCTs).[1–7] However, the improvement in oxygenation was not translated to mortality benefit in six out of the seven RCTs.[2–7] This indicates that factors other than mere improvement in oxygenation determine outcomes in moderate – severe acute respiratory distress syndrome (ARDS) patients who received PPV, like global lung strain and stress. Changes in driving pressure (DP) predicted survival in ARDS patients in the trial by Amato et al.[8] However, this study consisted of an important proportion of only mild ARDS patients.[8]

In a recent computational study on ARDS patients, investigators tried to establish a "link" between DP and survival outcomes. The dynamic lung strain or overdistension of newly recruited normal

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alveolar units and consequent cyclical alveolar strain during ventilation is a major factor causing ventilator-induced lung injury (VILI). The investigators concluded that this cyclical dynamic alveolar strain was linked to a higher DP and mortality.[9] The DP reduction from 21 cmH_2O to 12 cmH_2O lead to reduction in the repeated strain during opening and closing of alveolar units from 16 to <4% of the total lung.[9] Investigators had used a high-fidelity computational simulator of cardio-pulmonary pathophysiology, and concluded that cyclic alveolar strain along with tidal recruitment provides a reliable mechanistic understanding for proposed correlation between higher DP and mortality.[9] We hypothesized that the cyclical alveolar dynamic strain will be most relevant in patients of moderate-severe ARDS, as compared to mild-moderate ARDS.

The ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <100 with positive end expiratory pressure (PEEP) >5 cmH_2O is categorized as moderate–severe ARDS.[10] Despite using lower tidal volume (V_T) and lower plateau pressure (P_{plat}), moderate-severe ARDS can cause mortality of 60%.[11,12]

As PPV is known to recruit collapsed alveolar units and improve the mechanical characteristics of already opened alveolar units that locate a favorable position on the pressure-volume loop indicating more homogeneous ventilation and perfusion distribution.[13] This phenomenon can hypothetically lead to improvement in respiratory system compliance (C_{RS}). Driving pressure is also measured as a ratio between V_T and C_{RS} and hence DP is inversely proportional to C_{RS}.

In a patient requiring PPV, the DP can be measured at various time points such as before PPV, during the period of PPV, and after the session of PPV when the patient is again turned supine. There is a scarcity of literature regarding the utility of changes in DP post-PPV in moderate- severe ARDS patients as a predictor of outcomes and which of the DP at different time points (pre, during, and post-PPV) is the best predictor of mortality.

With this background, we aimed to determine the changes and the role of DP as compared to improvement in oxygenation (PaO_2/FiO_2) at different time points as predictors of mortality outcomes in moderate-severe ARDS patients with PPV.[14]

Primary Objective

To study the change in DP from pre-PPV to post-PPV in moderate-severe ARDS patients, as compared to the changes in oxygenation among the survivors and non-survivors.

Secondary Objectives

- To determine if it was the oxygenation (PaO_2/FiO_2) or the DP at different time points (pre, during, or post-PPV) which served as the most reliable predictor of mortality in patients with moderate-severe ARDS.
- To determine the cut-off values of either DP or PaO_2/FiO_2 after PPV, which reliably predicts a higher risk of mortality.

The primary outcome of the study is 28-day intensive care unit (ICU) mortality.

Methods

A prospective observational study was conducted at level III ICU of a tertiary care medical college from September 2020 to April 2023. After Institutional Ethics Committee (IEC: 765/2019) approval, the study was registered in India's Clinical Trial Registry (CTRI/2020/04/024940).

Inclusion Criteria

(i) All patients between age of 18 and 80 years with moderate-severe ARDS, as defined by Berlin definition and requiring PPV. (ii) Patients with PaO_2/FiO_2 <150 with PEEP >5 cmH_2O with FiO_2 of at least 0.6. (iii) On invasive mechanical ventilation. (iv) Within 48 hours of ARDS diagnosis.

Exclusion Criteria

Patients with (i) Coronavirus disease of 2019 (COVID-19) positive, (ii) documented barotrauma (air leak syndromes), (iii) penetrating chest injuries, (iv) planned for palliative care (v) pregnancy, (vi) absolute contraindication for PPV, (vii) PPV <16 hours duration during a single session.

Sample Size

Since it was a 3-year time period study on moderate-severe ARDS patients receiving PPV, *post-hoc* power of the study was calculated based on sample size. With mean DP post-PPV of 13.91 ± 1.74 cmH_2O among survivors ($n_1 = 22$) vs 19.70 ± 3.15 cmH_2O among the non-survivors ($n_2 = 30$), the *post-hoc* power as 95% as per the calculation below:

$$\text{Power} = \varphi \{Z1-\alpha/2 + \Delta/\sqrt{\sigma 1^2/n_1 + \sigma 2^2/n_2}\}$$

Where φ = Function converting a critical Z value to power

$Z1-\alpha/2 = 1.96$ for 95% CI, $\alpha = 0.05$

σ_1 and σ_2 = variance of mean n_1 and mean n_2

n_1 = number of survivors

n_2 = number of non-survivors

Data Collection

Every consecutive patient was screened for inclusion and exclusion criteria and informed consent was obtained prior to recruitment to study. The decision of PPV was based exclusively on the intensivist decision. Duration of PPV was minimum of 16 hours and its application was according to the PROSEVA trial.[15] During PPV, all patients received continuous neuromuscular blocking agents. Flowchart 1 depicts patient recruitment into the study.

Data collected were gender and age, APACHE II score, SOFA score, Murray lung injury score (LIS), ventilatory details like the mode, fraction of inspired oxygen (FiO_2), PEEP, and plateau pressure was collected at 3 time points:

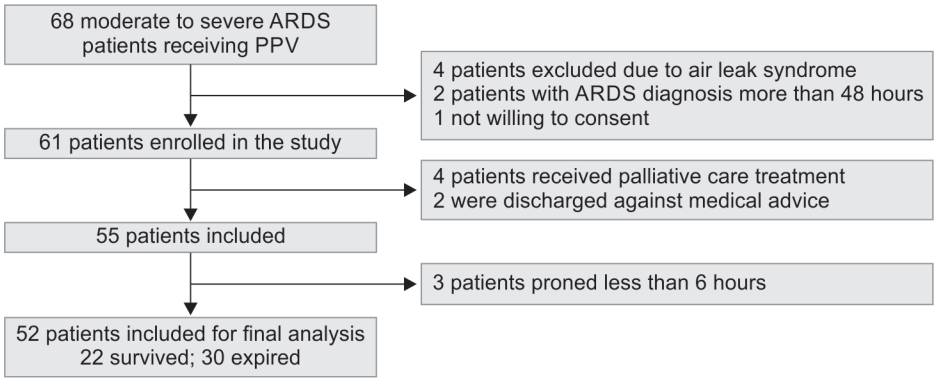
(i) Pre/Before PPV: In supine position just before PPV.
(ii) During the PPV: Measured in prone position between 6 and 8 hours after initiating PPV.
(iii) Post-PPV: Measured after 1 hour of repositioning to supine after PPV. The PaO_2 measured from the arterial blood gas (ABG) during the time points were utilized for calculation of PaO_2/FiO_2.

Measurement P_{plat} and DP: On volume-controlled mode, an inspiratory pause of 5 sec was applied to the mechanical breath. P_{plat} is displayed electronically as a digital display on the ventilator screen. P_{plat} is measured in a sedated and paralyzed patient with no spontaneous breathing effort. DP is the difference between P_{plat} and PEEP.

Statistical Analysis

Software IBM Statistical Package for Social Sciences (SPSS) version 28.0.1.1(15) (IBM Corp. Armonk, NY: IBM) was used for statistical analysis. Mean and standard deviation (SD) was used to express the parameters following parametric distribution and median

Flowchart 1: Flowchart depicting the patient recruitment into the study



with interquartile range (IQR) was used to express the parameters following non-parametric distribution. Independent student *t* test was used for comparison of the means of continuous variables in two groups namely survivors and non-survivors. To compare the medians of two groups, Mann–Whitney *U* test was used. For comparison of categorical variables of the two groups, Pearson's Chi-square test was used. Paired *t* test and Wilcoxon's Sign rank were used to compare the mean values and median values of pre and post-PPV that followed parametric and non-parametric distribution, respectively.

The Regression model was developed based on six pre-determined variables of DP and PaO_2/FiO_2 ratio at three different time points, before, during, and after the sessions of PPV, as per study objective. Further, multivariate logistic regression was performed considering which of the six variables were found significant in univariate analysis, with a $p < 0.2$. For variables significant in multivariable logistic regression, a receiver operating characteristic (ROC) curve was plotted to determine the area under the cure (AUC) and the cut off, sensitivity, specificity, *p*-value, and 95% confidence interval (CI) were calculated to predict survival benefit. Survival analysis was done using Kaplan–Meier survival plot and Log rank (Mantel Cox) test for values above and below the cut off value to determine survival. The *p*-value < 0.05 was considered statistically significant. Cox proportional regression for survival data was done and hazard ratio (HR) was calculated.

Results

A total of 52 patients with moderate-severe ARDS receiving PPV were included in the study within the study period. The 28-day ICU mortality was 57%. The median and IQR in hours of PPV were 18 (16–32). Demographic details and study variables are depicted in Table 1.

Table 2 shows comparison of parameters between survivors and non-survivor and shows that DP and PaO_2/FiO_2 pre, during, and post-PPV were significant between the survivors and non-survivors along with SOFA score and LIS. Table 3 compares DP and PaO_2/FiO_2 pre- and post-PPV among survivors and non-survivors separately. It depicts that though there was a significant improvement in the PaO_2/FiO_2 among non-survivors pre- and post-PPV, there was no significant improvement in the DP (Table 3). Among the survivors, however, there was a significant improvement in both the parameters DP and PaO_2/FiO_2 post-PPV as compared to pre-PPV (Table 3).

Univariate and multivariate logistic regression was performed to determine if it was the change in PaO_2/FiO_2 or the change in DP that was the most reliable predictor of mortality. The DP and PaO_2/FiO_2 values pre, during, and post-PPV as predictors of mortality showed that it was the DP post-PPV that was the best predictor of mortality [OR 3.24, 95% CI (1.033–10.158), *p*-value < 0.001] (Table 4).

The ROC curve plotted for DP after PPV as a predictor of mortality (Fig. 1) showed that post-PPV DP >16 cmH_2O was a reliable predictor of mortality, AUC 0.939, 95% CI (0.868–0.999) with sensitivity and specificity as 90 and 82%, respectively. Among the patients who had high DP ≥ 16 cmH_2O after the last prone session,

Table 1: The demographic characteristics of the study participants (*N* = 52)

Variables	*Values*
Gender males, *N* (%)	33 (63.46%)
ARDS source pulmonary, *N* (%)	29 (55.8%)
ARDS source extrapulmonary, *N* (%)	23 (44.2%)
Total PPV session once only, *N* (%)	29 (55.8%)
Total PPV sessions two times, *N* (%)	17 (32.7%)
Total PPV sessions three times, *N* (%)	6 (11.5%)
Hours of PPV [median (IQR)]	18 (16–32)
Survival, *N* (%)	22 (42.3%)
Age (years), Mean ± SD	45.23 ± 13.08
APACHE II score, Mean ± SD	15.81 ± 5.16
SOFA score, Mean ± SD	8.92 ± 3.92
LIS, Mean ± SD	2.93 ± 0.57
DP pre-PPV (cmH_2O), Mean ± SD	18.13 ± 3.27
DP during PPV (cmH_2O), Mean ± SD	17.37 ± 3.68
DP post-PPV (cmH_2O), Mean ± SD	17.25 ± 3.95
PaO_2/FiO_2 pre-PPV, Median (IQR)	89.50 (68–108.25)
PaO_2/FiO_2 during PPV, Median (IQR)	137 (112.30–187.25)
PaO_2/FiO_2 post-PPV, Median (IQR)	125 (98–216.25)
MV days, Median (IQR)	8.50 (5–13.75)
LOS ICU (days), Median (IQR)	9 (6–14.75)
LOS hospital (days), Median (IQR)	13.50 (6.25–20.75)

APACHE II score, acute physiology and chronic health evaluation II score; ARDS, acute respiratory distress syndrome; DP, driving pressure; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; LIS, Murray lung injury score; MV, mechanical ventilation; PaO_2/FiO_2 ratio, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; PPV, prone position ventilation; SD, standard deviation; SOFA, sequential organ failure assessment

Table 2: Comparison of the parameters between the survivors and non-survivors in the study

Variables	*Survivors (n = 22)*	*Non-survivors (n = 30)*	*p-value*
Age (years)	43.73 ± 14.13	46.33 ± 13.70	0.507*
APACHE II score	14.86 ± 5.76	16.50 ± 5.13	0.263*
Duration of PPV (hours)	32 (16–32)	18 (18–32)	0.400**
SOFA score	**6.86 ± 2.71**	**10.43 ± 4.00**	**<0.001***
LIS	**2.71 ± 0.45**	**3.09 ± 0.59**	**0.008***
DP pre-PPV, (cmH_2O)	**16.36 ± 2.57**	**19.43 ± 3.16**	**<0.001***
DP during PPV, (cmH_2O)	**14.36 ± 1.96**	**19.57 ± 2.87**	**<0.001***
DP post-PPV, (cmH_2O)	**13.91 ± 1.74**	**19.70 ± 3.15**	**<0.001***
PaO_2/FiO_2 pre-PPV	92.75 (67.5–117.75)	87.90 (67.75–100.75)	0.511**
PaO_2/FiO_2 during PPV	**122 (162.50–218.50)**	**104.75 (163.75)**	**0.028****
PaO_2/FiO_2 post-PPV	**205.50 (116.25–244.50)**	**112 (88.0–146.50)**	**0.003****
LOS (ICU) (days)	**11 (7–20)**	**8 (4–11)**	**0.009****
ARDS pulmonary cause	13 (44.8%)	16 (55.2%)	0.781#

*Independent Student *t*-test; **Mann–Whitney *U*-test; #Chi-square test; APACHE II score, acute physiology and chronic health evaluation II score; ARDS, acute respiratory distress syndrome; DP, driving pressure; LIS, Murray lung injury score; PPV, prone position ventilation; PaO_2/FiO_2, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; SOFA, sequential organ failure assessment

Table 3: The DP and PaO_2/FiO_2 pre- and post-PPV session in both survivors and non-survivors

	Survivors	
Variables (n = 22)	*Values*	*p-value*
DP pre-PPV (cmH_2O), Mean ± SD	16.36 ± 2.57	<0.001*
DP post-PPV (cmH_2O), Mean ± SD	13.91 ± 1.74	
PaO_2/FiO_2 pre-PPV, Median (IQR)	92.75 (67.5–117.75)	<0.001**
PaO_2/FiO_2 post-PPV session, Median (IQR)	205.50 (116.25–244.50)	
	Non-survivors	
Variables (n = 30)	*Values*	*p-value*
DP pre-PPV (cmH_2O), Mean ± SD	19.43 ± 3.16	0.318*
DP post-PPV (cmH_2O), Mean ± SD	19.70 ± 3.15	
PaO_2/FiO_2 pre-PPV, Median (IQR)	87.90 (67.75–100.75)	<0.001**
PaO_2/FiO_2 post-PPV, Median (IQR)	112 (88.0–146.50)	

*Paired *T*-test; **Wilcoxon Signed Ranks test; DP, driving pressure; IQR, interquartile range; PaO_2/FiO_2 ratio, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; PPV, prone position ventilation; SD, Standard deviation

87% expired, whereas for those who had DP <16 cmH_2O, only 13% expired ([$p < 0.001$], Chi-square test' Phi and Cramer V strength of association is 0.644) indicating a very strong association between post-PPV DP >16 cmH_2O and mortality.

Comparison of Kaplan–Meier survival function (Fig. 2) between patients with DP <16 cmH_2O and DP ≥16 cmH_2O post-PPV session was significantly different with Log–rank (Mantel–Cox) $p < 0.001$. The mean survival times with DP post-PPV <16 cmH_2O was 29.96 days with 95% CI (23.34–36.57), whereas it was significantly lesser at 12.11 with 95% CI (7.18–17.05) in those with DP ≥ 16 cmH_2O post-PPV session. Cox proportional model comparing the mortality outcomes between patients with DP post-PPV <16 cmH_2O vs DP post-PPV ≥16 cmH_2O showed HR of 6.583 ($p < 0.001$, 95% CI [2.271–19.082]).

Figure 3 depicts the values of post-PV of DPs among the survivors and non-survivors. A majority of patients who had expired had post-PPV DP >16 cmH_2O.

Discussion

One of the criteria for cessation of PPV in PROSEVA trial was based on the improvement in oxygenation (PaO_2/FiO_2) ratio.[15] However, the PaO_2/FiO_2 has been shown to be an imprecise predictor of mortality in ARDS.[16] The AUC of oxygenation to predict mortality in ARDS is just 0.577. Recently, it has been shown that it is not the PaO_2/FiO_2 but rather the incorporation of PEEP in this ratio, which

Table 4: Univariate and multivariable regression analysis of the DP and PaO_2/FiO_2 pre, during and post-PPV session as the best predictor of mortality

	Univariate analysis			*Multivariable logistic regression*		
Variable	*p-value*	*OR*	*95% CI*	*p-value*	*Adjusted OR*	*95% CI*
DP pre-PPV (cmH_2O)	0.003	1.51	1.55–1.97	0.497	1.193	0.716–1.988
DP during PPV (cmH_2O)	<0.001	2.02	1.41–2.91	0.486	0.673	0.716–1.988
DP post-PPV (cmH_2O)	**<0.001**	**2.25**	**1.45–3.48**	**0.044**	**3.24**	**1.033–10.158**
PaO_2/FiO_2 pre-PPV	0.525	0.996	0.981–1.009	0.153	1.021	0.992–1.050
PaO_2/FiO_2 during PPV	0.013	0.987	0.977–0.997	0.373	0.992	0.975–1.009
PaO_2/FiO_2 post-PPV	0.004	0.987	0.978–0.996	0.425	0.995	0.981–1.008

CI, confidence interval; DP, driving pressure; PPV, prone position ventilation; PaO_2/FiO_2 ratio, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; OR, odds ratio

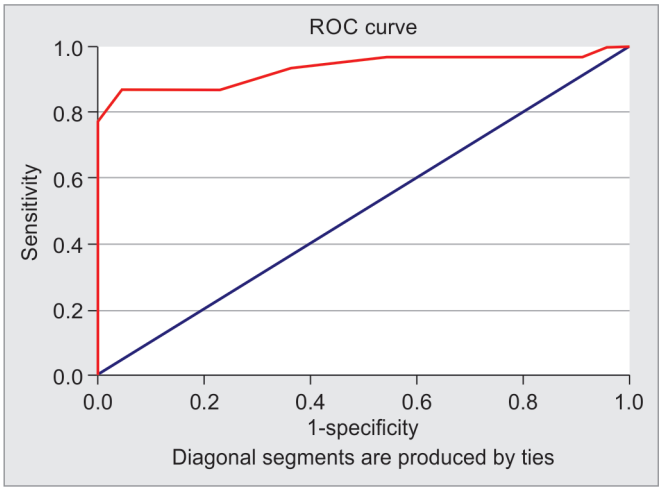


Fig. 1: The ROC of the DP post-PPV session as a predictor of outcome in ARDS patients who required prone ventilation. [DP cut-off ≥16 cm H_2O, AUC 0.939, 95% CI (0.868–0.999), 90% sensitivity, 82% specificity]
ARDS, acute respiratory distress syndrome; AUC, area under the ROC curve; CI, confidence interval; DP, driving pressure, ROC, receiver operating characteristics

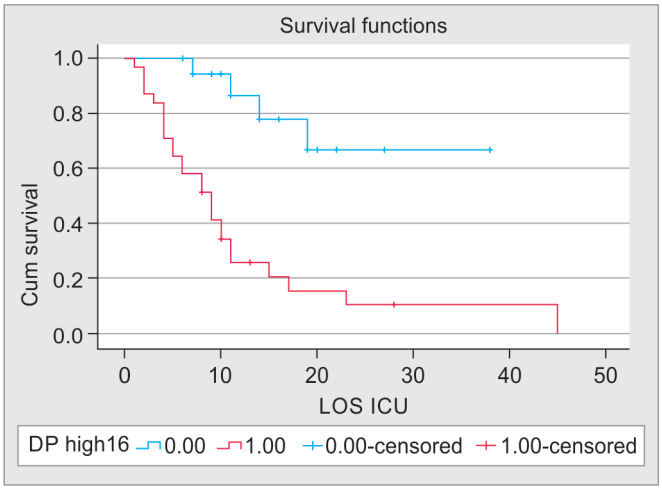


Fig. 2: Comparison of Kaplan–Meier survival function between patients with DP <16 cmH_2O vs patients with DP ≥16 cmH_2O post-PPV session
DP, driving pressure; PPV, prone position ventilation

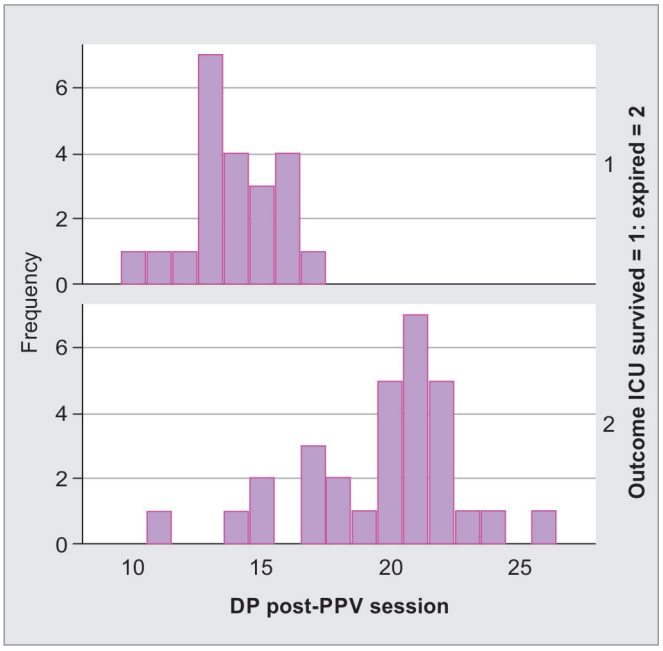


Fig. 3: Chart depicting that most of patients with post-PPV DP ≥16 cmH_2O expired and patients with post-PPV DP <16 cmH_2O survived
DP, driving pressure; PPV, prone position ventilation

is a much better predictor of mortality, and more so in moderate-severe ARDS.[17]

Amato et al. proved that DP is an independent predictor of survival among the ventilator and oxygenation parameters in ARDS patients.[8] Subsequently, it has been said that DP <15 cmH_2O should prompt clinicians to continue the same ventilator strategy. However, a DP ≥15 cmH_2O should prompt modifications in ventilator strategies as it indicated worsening C_{RS}.[18]

Despite this evidence, we tend to target PaO_2/FiO_2 to decide whether or not moderate-severe ARDS patients need initiation and cessation of PPV, rather than DP.[15] To date, no safe limit of DP has been suggested during PPV strategies, regarding when the further requirement of PPV will be necessitated or considered unnecessary.[19] We found that it is not PaO_2/FiO_2 improvement after PPV sessions, but rather the significant reduction in DP which is the independent predictor of survival in moderate-severe ARDS. Among the values of PaO_2/FiO_2 and DP pre, during, and post-PPV, it is DP ≥ 16 cmH_2O after the last session of PPV which is the independent predictor of mortality in moderate-severe ARDS receiving PPV.

The findings of our study are congruent with the recommendations by Bugedo et al. and Fanelli et al., where the authors recommend a DP < 15 cmH_2O as a possible target while optimizing ventilator strategies in moderate-severe ARDS patients.[18–20]

The findings of our study that DP ≥ 16 cmH_2O despite PPV predicts poor outcomes may be due to the fact that a higher DP not only reflects poor C_{RS}, but also promotes pathophysiological alterations like right ventricular failure and cor pulmonale, ventilator-induced pulmonary hypertension, rise in pulmonary vascular permeability, pulmonary epithelial cell apoptosis, ferroptosis, rise in inflammatory mediators like interleukin-6 (IL-6), and tumor necrosis factor – alpha (TNF-α).[21,22] The cascade of all these pathophysiological process is hastened by high DP, and may be the reason why high DP may be a predictor of mortality.[23]

The DP reflects both cyclical strain and stress to which the alveoli are exposed during each ventilator cycle, actually consists of two distinct pressures, the transpulmonary pressure, and the pressure applied to the chest wall as well.[24] It is one of the important variables included in calculation of mechanical power (MP) of the ventilator.[18] Thus, the importance of DP has been well validated. However, two aspects were not investigated. First, it was unclear at which time point, before, during, or post-PPV session should the DP value be considered a predictor of outcomes. Secondly, whether clinicians should seek to look at the improvement in oxygenation or reduction in DP for determining the success of PPV, and thereby survival outcomes or further alternative treatment modalities along with PPV, like extracorporeal membrane oxygenation (ECMO). We determined that a DP ≥ 16 cmH_2O post-PPV predicted mortality and not PaO_2/FiO_2 post-PPV. Higher DP is harmful even for shorter

durations, the importance of determination of a DP cut-off for initiation of venovenous ECMO among non-responders of PPV has to be investigated.[25,26]

Though the initial mean PaO_2/FiO_2 of patients in our study in both survivors and non-survivors before PPV initiation was quite similar (92 vs 88), there was a difference between the initial DP (16 vs 19 cmH_2O). However, even during and post-PPV sessions, the DP did not reduce among the non-survivors. This meant that the lung had more non-recruitable areas which could not be recruited even during proning sessions. Thus, a lack of decrease in DP even during and post-PPV could indicate the futility or non-responders of PPV maneuver. This is significant in light of the fact that PPV also has its own complications like, pressure ulcers, bleeding from oro-nasal sites and accidental extubations.[27] Thus, clinicians should be aware of PPV non-responders and avoid complications and futility of PPV in those patients. Rather, much more novel therapeutics like ECMO during PPV may be contemplated in such patients rather than repeated PPV sessions, without any reduction in DP.[28] Early PPV after even initiation of ECMO has been shown to improve survival.[29] Thus, in the light of the findings of our study, sole PPV non-responders as depicted by no reduction in DP may be administered different strategies to improve survival outcomes.

During ECMO, low V_T <4 mL/Kg ideal body weight as ultra-protective ventilation reduces VILI.[30] This shows than reduction dynamic cyclical alveolar overdistension of non-recruitable alveoli, which is mechanistically related to DP reduction, definitely has beneficial outcomes in VILI reduction.

Prone position ventilation is inexpensive and readily available maneuver that has proven to have better outcome in patients with ARDS by improving the ventilation perfusion mismatch, reducing the risk of VILI and improving the lung mechanics.[15,31]

The reduction of DP from pre- to post-PPV was found to be approximately –3 cmH_2O in survivors. In non-survivors, the DP from pre- to post-PPV remained same without any reduction. This implies that the response to PPV is due to the resultant of improved C_{RS}. Our findings are consistent with the findings by Van Meenen et al. where they studied pre- and post-PPV effects of DP, PaO_2/FiO_2, and dead space and found that the changes in only DP were significant to predict outcomes in ARDS.[32] This study was done only during the first PPV session unlike ours, and the DP during the PPV session was not analyzed. The AUC for DP to predict mortality was also low (0.63). Prior, few studies that compared pre- and post-PaO_2/FiO_2 values in PPV did not find prognostic significance of PaO_2/FiO_2. They found that the PaO_2/FiO_2 improvement was significant between responders and non-responders which was concurrent with our findings.[12–14] Guerin et al. concluded that though PPV improves oxygenation and ventilation and reduces mortality, there was no association between them.[7,33] This infers that the better prognosis in ARDS patients receiving PPV is due to the ability of PPV to reduce VILI.[34,35]

Certain strengths of our study included a very homogeneous population of patients with only moderate-severe ARDS who received PPV, in whom lung compliance and mechanics matter the most. We could conclusively prove that the DP post-PPV (as compared to the PaO_2/FiO_2 ratios at any time point or DP at prior time points) is an independent predictor of mortality in moderate-severe ARDS.

This study limitations are that it was single centered with a smaller sample size. We did not assess right ventricular function, which could have worsened in patients with higher DP, and could have been a factor contributing to the mortality. Being an observational study, not all the patients underwent an equal number of PPV sessions.

Conclusion

Driving pressure is a better discriminant of survival among moderate-severe ARDS patients on PPV, as compared to oxygenation. Moderate-severe ARDS patients with post-PPV session DP ≥16 cmH_2O have a HR of 6.5 times for mortality as compared to those with DP <16 cmH_2O. In future, multicenter study with large sample size with DP along with MP is required to confirm the findings of this study.

Data Availability

The data will be provided by the first or corresponding author upon e-mail request. This is due to the reason of patient data confidentiality.

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