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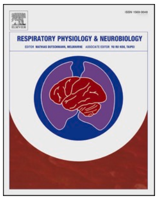

Short communication

Hemodynamic response to positive end-expiratory pressure and prone position in COVID-19 ARDS

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ABSTRACT

Background: Use of high positive end-expiratory pressure (PEEP) and prone positioning is common in patients with COVID-19-induced acute respiratory failure. Few data clarify the hemodynamic effects of these interventions in this specific condition. We performed a physiologic study to assess the hemodynamic effects of PEEP and prone position during COVID-19 respiratory failure.
Methods: Nine adult patients mechanically ventilated due to COVID-19 infection and fulfilling moderate-to-severe ARDS criteria were studied. Respiratory mechanics, gas exchange, cardiac output, oxygen consumption, systemic and pulmonary pressures were recorded through pulmonary arterial catheterization at PEEP of 15 and 5 cmH_2O, and after prone positioning. Recruitability was assessed through the recruitment-to-inflation ratio.
Results: High PEEP improved PaO_2/FiO_2 ratio in all patients ($p = 0.004$), and significantly decreased pulmonary shunt fraction ($p = 0.012$), regardless of lung recruitability. PEEP-induced increases in PaO2/FiO2 changes were strictly correlated with shunt fraction reduction (rho=-0.82, $p = 0.01$). From low to high PEEP, cardiac output decreased by 18 % ($p = 0.05$) and central venous pressure increased by 17 % ($p = 0.015$).
As compared to supine position with low PEEP, prone positioning significantly decreased pulmonary shunt fraction ($p = 0.03$), increased PaO_2/FiO_2 ($p = 0.03$) and mixed venous oxygen saturation ($p = 0.016$), without affecting cardiac output. PaO_2/FiO_2 was improved by prone position also when compared to high PEEP ($p = 0.03$).
Conclusions: In patients with moderate-to-severe ARDS due to COVID-19, PEEP and prone position improve arterial oxygenation. Changes in cardiac output contribute to the effects of PEEP but not of prone position, which appears the most effective intervention to improve oxygenation with no hemodynamic side effects.

1. Background

Severe COVID-19-induced respiratory resembles classical acute respiratory distress syndrome (ARDS) (Grasselli et al., 2020a; Grieco et al., 2020; Santamarina et al., 2020), but may show specific features (Gattinoni et al., 2020). High positive end-expiratory pressure (PEEP) and prone positioning are widely used strategies in these patients (Grasselli et al., 2020b).

The hemodynamic consequences of these interventions have not been systematically described in COVID-19 ARDS. We conducted a study to assess the effects of high PEEP and prone position on hemodynamic parameters in COVID-19 patients with moderate-to-severe ARDS.

2. Methods

This study was conducted in an Intensive Care Unit in Italy between March 15th and 30th, 2020. Ethical approval for this study (Ethical Committee N° UCSC915920/20) was provided by the Ethical Committee

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Abbreviations: ARDS, acuterespiratory distress syndrome; PEEP, positive end-expiratory pressure.

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of Fondazione Policlinico A. Gemelli IRCCS, Rome, Italy (Chairperson Prof G. Sica) on March 10th, 2020. Informed consent was obtained according to committee recommendations. We enrolled consecutive adult patients receiving invasive mechanical ventilation due to COVID-19 induced moderate-to-severe ARDS, who were equipped with a pulmonary artery catheter as per clinical decision. ARDS was defined according to the Berlin definition, with PaO_2/FiO_2 measured at a PEEP = 5 cmH_2O.

Mechanical ventilation was applied in the volume-controlled mode during continuous sedation and paralysis, with the following settings: tidal volume 6 mL/kg of predicted body weight, respiratory rate to achieve a $PaCO_2$ allowing pH > 7.30 and FiO_2 to obtain SpO_2 between 92 %–96 %.

Two PEEP levels were tested in sequential order: 15 cmH_2O or the highest PEEP to obtain plateau pressure$\leq$28 cmH_2O (high PEEP) and a PEEP of 5 cmH_2O (low PEEP). Respiratory rate and FiO_2 were kept unchanged. A single-breath derecruitment maneuver was performed to assess recruitability: recruitment-to-inflation ratio was calculated. Patients with recruitment-to-inflation ratio greater than 0.5 were considered as highly recruitable (Chen et al., 2020).

Respiratory and hemodynamic parameters were collected after 30 min at each PEEP level and, eventually, after 1 h of prone positioning. The decision on whether to prone or not was taken by the attending physician, independently from the study protocol.

Pulmonary shunt fraction in the three study phases was the primary endpoint.

Differences in continuous variables between study phases were assessed with non-parametric tests for paired samples (i.e. one-way Friedman ANOVA or Mann-Whitney test and Wilcoxon signed-rank test for paired measure). Categorical data were compared with Fisher's exact test. Correlation between variables was explored with Spearman's test (rho and p-value are provided). Results with two-sided $p \leq 0.05$ were considered statistically significant.

Assuming a pulmonary shunt fraction of 50 % at low PEEP(Dantzker et al., 1979), we estimated that enrolment of 9 patients would provide 85 % power in demonstrating an absolute reduction in pulmonary shunt fraction of 15 % with either high PEEP and/or prone position, with an alpha level set at 0.05.

3. Results

Nine patients were enrolled. Eight (89 %) were males and the median [Interquartile range] age was 65 [62–75] years. Median simplified acute physiology II score and SOFA were 41 [32–58] and 8 [5–9], respectively. Median PaO_2/FiO_2 at low PEEP was 96 mmHg [77–134]. Seven patients (77 %) were receiving norepinephrine, with a median dosage of 0.2 [0.2−0.4] mcg/kg/min: this was kept constant throughout all the study. Median recruitment-to-inflation ratio was 0.51 and five patients (56 %) were considered as highly recruitable. Six patients (67 %) underwent prone positioning.

Main study results are displayed in Table 1.

As compared to supine position with low PEEP, prone positioning significantly decreased pulmonary shunt fraction ($p = 0.03$), increased PaO_2/FiO_2 ($p = 0.03$) and mixed venous oxygen saturation ($p = 0.016$), without affecting cardiac output. PaO_2/FiO_2 was improved by prone position also when compared to high PEEP ($p = 0.03$) (Fig. 1).

Pulmonary shunt fraction had a reverse correlation with PaO_2/FiO_2 ratio, both at low PEEP (rho = −0.70, $p = 0.05$) and high PEEP (rho = −0.83, $p < 0.01$). High PEEP improved PaO_2/FiO_2 ratio in all patients ($p = 0.004$), and significantly decreased pulmonary shunt fraction ($p = 0.012$), regardless of lung recruitability (Fig. 1, top). PEEP-induced changes in PaO_2/FiO_2 changes were strictly correlated with shunt fraction modifications (rho = −0.82, $p = 0.01$-Fig. 2). From low to high PEEP, cardiac output decreased by 18 % ($p = 0.05$) and central venous pressure increased by 17 % ($p = 0.015$).

Table 1
Main results of the study.

	Low PEEP (n = 9)	High PEEP (n = 9)	Prone position (n = 6)	P value
Pulmonary shunt fraction (Qs/Qt), %	55 [47−59]	34 [30−52]	32 [15−35]	**0.016**$^{\#\S}$
PaO_2/FiO_2, mmHg	96 [77−149]	145 [105−199]	171 [160−320]	**0.002**$^{\#\S*}$
Heart rate, beats/minute	91 [87−98]	90 [85−99]	96 [85−119]	0.664
Systemic systolic arterial pressure, mmHg	129 [120−144]	113 [100−132]	127 [119−130]	0.069
Systemic diastolic arterial pressure, mmHg	56 [45−63]	52 [46−60]	64 [57−67]	0.094
Systemic mean arterial pressure, mmHg	76 [72−85]	70 [65−81]	80 [74−90]	0.311
Pulmonary systolic arterial pressure, mmHg	33 [23−50]	33 [27−46]	35 [29−53]	1.000
Pulmonary diastolic arterial pressure, mmHg	18 [10−20]	18 [14−19]	21 [15−25]	0.422
Pulmonary mean arterial pressure, mmHg	24 [16−30]	24 [20−29]	27 [22−42]	0.568
Central venous pressure, mmHg	7 [5−8]	9 [7−11]	10 [6−14]	0.070
Pulmonary capillary wedge pressure, mmHg	11 [8−12]	12 [8−14]	14 [10−19]	0.065
Systemic vascular resistances, dyn*s/cm^5	800 [606−922]	837 [679−972]	707 [339−892]	0.247
Pulmonary vascular resistances, dyn*s/cm5	128 [91−227]	162 [96−268]	162 [79−539]	0.449
Cardiac output, L/min	7.0 [6.1−9.2]	5.5 [5.0−7.5]	6.9 [5.7−8.7]	**0.015**$^{\#}$
Stroke volume, mL	75 [68−91]	61 [55−78]	74 [55−83]	0.074
Plasma lactates (mmol/L)	1.3 [0.8−1.6]	1.0 [0.7−1.7]	1.1 [0.8−1.6]	0.819
Mixed venous oxygen saturation (SvO_2), %	73 [69−77]	79 [77−81]	82 [80−84]	**0.016**$^{\#\S}$
Venous to arterial PCO_2 gap, mmHg	4.8 [3.9−6.7]	6.0 [3.5−7.0]	3.9 [0−6.6]	0.368
Venous to arterial PCO_2 gap / arterial to venous oxygen content ratio	1.50 [1.28−2.60]	2.00 [1.16−2.95]	1.76 [1.43−2.97]	1.000
Oxygen delivery (DO_2), mL/min	1069 [924−1363]	927 [807−1181]	1141 [993−1384]	**0.041**$^{\#}$
Oxygen consumption (VO_2), mL/min	189 [133−264]	181 [118−236]	210 [147−242]	0.819
DO_2/VO_2	5.83 [4.97−7.04]	5.65 [4.77−6.86]	6.40 [5.23−6.87]	0.247
Oxygen extraction ratio, %	15.5 [12.3−18.8]	15.3 [13.3−20.3]	14.5 [3.2−17.1]	0.197
Arterial O_2 content, mL/dL	15.2 [14.2−16.3]	16.6 [14.6−19.0]	16.4 [15.7−17.6]	**0.011**$^{\#}$
Venous O_2 content, mL/dL	12.2 [11.7−13.5]	13.5 [12.1−15.6]	13.7 [13.1−14.4]	**0.009**$^{\#}$
Arterial pCO_2, mmHg	46 [37−52	49 [38−57	48 [38−53]	0.311
Compliance, mL/cmH_2O	51 [41−54]	48 [38−48]	45 [39−49]	0.385
Ventilatory ratio	2.2 [1.7−2.4]	2.2 [1.8−2.7]	2.4 [1.8−2.5]	0.311

Data are expressed as median [Interquartile range].
$^{\#}$Indicates $p < 0.05$ for the paired comparison high PEEP vs. low PEEP.
§Indicates $p < 0.05$ for the comparison prone position vs. low PEEP.
*Indicates $p < 0.05$ between prone position vs. PEEP high.

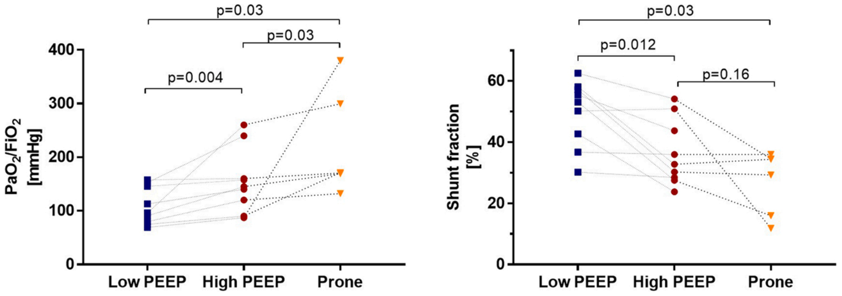

Fig. 1. PaO_2/FiO_2 and pulmonary shunt fraction in the three study phases. Individual data are displayed.

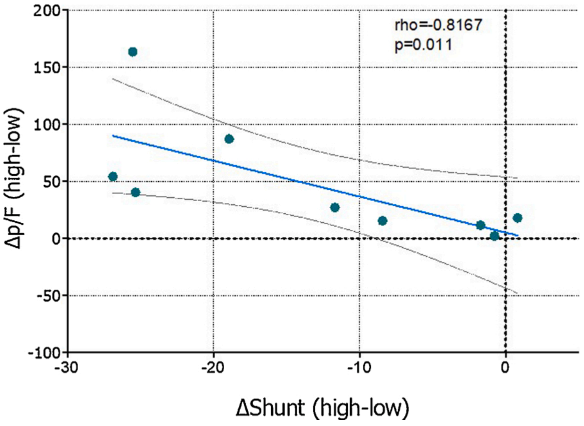

Fig. 2. PEEP-induced changes in PaO_2/FiO_2 ($\Delta P/F$) are tightly correlated by the reduction in pulmonary shunt fraction (ΔShunt) caused by PEEP.

4. Discussion

This physiologic study shows that, in moderate-to-severe COVID-19 ARDS, the effects of PEEP and prone position on PaO_2/FiO_2 are causally related to changes in pulmonary shunt fraction. PEEP and prone position are both capable of reducing shunt fraction, thereby improving oxygenation. PEEP-induced effects on oxygenation are in part mediated by reduction in cardiac output, independently from alveolar recruitment. The improvement in oxygenation obtained with prone position is greater than that caused by high PEEP.

Differently from what initially hypothesized (Gattinoni et al., 2020), raising evidence indicates that respiratory mechanics of COVID-19 patients resembles ARDS of other etiologies (Grieco et al., 2020, 2017; Haudebourg et al., 2020). Also, COVID-19 patients show a hyperdynamic hemodynamic profile, which is similar to that of patients suffering from ARDS of other causes (Caravita et al., 2020). Indeed, in COVID-19 patients, the hyperdynamic hemodynamic profile may, at least in part, be caused by pulmonary vascular neoangiogenesis and loss of hypoxic vasoconstriction (Ackermann et al., 2020).

Our results suggest that COVID-19 respiratory failure follows ARDS physiology also in terms of hemodynamic response to commonly applied interventions, as PEEP and prone position.

Pulmonary shunt fraction represents the amount of blood flowing in capillaries of non-ventilated alveoli; this causes venous admixture, yielding reduced arterial oxygen content. PEEP can recruit non-ventilated areas, thereby reducing shunt fraction and ameliorating arterial oxygen saturation (Langer et al., 2021). Recruitability is inter-individually variable: PEEP-induced improvement in shunt fraction is conventionally expected only in case of high recruitability (Gattinoni et al., 2006). In our study, we observed PEEP-induced shunt reduction and consistent increases in PaO_2/FiO_2 in all patients. In patients with low recruitability, reduced shunt fraction due to low cardiac output explains the PEEP-induced improvement in oxygenation (Chen et al., 2020; Spinelli et al., 2019). PEEP-induced reduction in cardiac output occurs because of increased right ventricle afterload due to compression of pulmonary vessels and increased intrathoracic pressure (Mekontso Dessap et al., 2009). In our cohort, the oxygenation response to PEEP was prominent, despite variable recruitability: this indicates that improvement in oxygenation due to PEEP does not necessarily reflect alveolar recruitment.

In our patients, prone position reduced shunt fraction and improved oxygenation, without hemodynamic side effects. Importantly, oxygenation was improved by prone position even when compared to high PEEP. Because cardiac output was unmodified, the effect of prone position is likely driven by improvement in ventilation to perfusion ratio due to recruitment of dependent areas, which is consistent with ARDS pathophysiology (Langer et al., 2021; Pelosi et al., 1998). Also, gravitational redistribution of blood flow towards normally ventilated area could have contributed to the effect of prone position on shunt fraction and oxygenation (Abou-Arab et al., 2021).

Despite the small sample, which is a limitation of the present investigation, this preliminary report suggests that in moderate-to-severe COVID-19-induced ARDS, PEEP and prone position improve oxygenation by reducing pulmonary shunt fraction. The effect of PEEP on these parameters is not only dependent on alveolar recruitment, but also caused by significant reduction in cardiac output. Changes in cardiac output contribute to the effects of PEEP but not of prone position, which appears the most effective intervention to improve oxygenation with no hemodynamic side effects.

Availability of data and material

Data available can be obtained from the corresponding author.

Authors' contribution

AMD, DLG and SC conceived the work, had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the analysis and drafted the manuscript.

MC, CS, FB, DN and EST screened patients for eligibility and collected data.

PDS, MGB, GDP and MA reviewed the paper and contributed in critical revision of the article for important intellectual content.

All authors agreed on submitting the manuscript to Respiratory physiology and neurobiology.

Declaration of Competing Interest

All authors declare that no conflict of interests exists regarding the material discussed in the manuscript.

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