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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 cmH2O, and after prone positioning. Recruitability was assessed through the recruitment-to-inflation ratio.

Results: High PEEP improved PaO2/FiO2 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 PaO2/FiO2 (p = 0.03) and mixed venous oxygen saturation (p = 0.016), without affecting cardiac output. PaO2/FiO2 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

Abbreviations: ARDS, acute respiratory distress syndrome; PEEP, positive end-expiratory pressure.
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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\(_2\) in all patients (p = 0.001), 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 (Qx/Qt), %** | 55 [47–59] | 34 [30–52] | 32 [15–35] | 0.01** |
| **PaO\(_2\)/FiO\(_2\), mmHg** | 96 [77–149] | 145 [105–199] | 171 [110–320] | 0.002** |
| **Heart rate, beats/minute** | 91 [87–98] | 90 [85–99] | 96 [85–119] | 0.66 |
| **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] | 0.31 |
| **Pulmonary systolic arterial pressure, mmHg** | 33 [23–50] | 33 [27–46] | 35 [29–53] | 1.00 |
| **Pulmonary diastolic arterial pressure, mmHg** | 18 [10–20] | 18 [14–19] | 21 [15–25] | 0.42 |
| **Pulmonary mean arterial pressure, mmHg** | 24 [16–30] | 24 [20–29] | 27 [22–42] | 0.56 |
| **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] | 0.24 |
| **Pulmonary vascular resistances, dyn*s/cm\(^5\)** | 128 [91–227] | 162 [96–268] | 162 [79–539] | 0.44 |
| **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** |
| **Venous to arterial PO\(_2\) gap, mmHg** | 4.8 [3.9–6.7] | 6.0 [3.5–7.0] | 3.9 [0–6.6] | 0.36 |
| **Venous to arterial PO\(_2\) 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] | 1.00 |
| **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 [12.2–17.1] | 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 pO\(_2\), mmHg** | 46 [37–52] | 49 [38–57] | 48 [38–53] | 0.31 |
| **Compliance, mL/cmH\(_2\)O** | 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] | 0.31 |

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.
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 vasconstriction (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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References

Abou-Arab, O., Haye, G., Beyk, C., Huette, P., Roger, P.-A., Guilbart, M., Bemasinski, M., Besserre, P., Trojette, F., Dupont, H., Jouineaux, V., Mahjoub, Y., 2021. Hypoxemia and prone position in mechanically ventilated COVID-19 patients: a prospective cohort study. Can. J. Anaesth. 68, 262–263. https://doi.org/10.1007/s12630-020-01844-9.

Ackermann, M., Verleden, S.E., Kuehnel, M., Haverich, A., Welte, T., Laenger, F., Vanstapel, A., Werlein, C., Stark, H., Tzanak, A., Li, W.W., Li, W.V., Menter, S.J., Jonigk, D., 2020. Pulmonary vascular endotheliolysis, thrombosis, and angiogenesis in Covid-19. N. Engl. J. Med. 383, 120–128. https://doi.org/10.1056/NEJMoa215432.

Caravita, S., Baratto, C., Di Marco, F., Calabrese, A., Balestreri, G., Russo, F., Faini, A., Soranna, D., Perigo, G.B., Badano, L.P., Grazziol, L., Lorini, F.L., Parati, G., Senni, M., 2020. Haemodynamic characteristics of COVID-19 patients with acute respiratory distress syndrome requiring mechanical ventilation. An invasive assessment using right heart catheterization. Eur. J. Heart Fail. 22, 2228–2237. https://doi.org/10.1002/ejhf.2058.

Chen, L., Del Sorbo, L., Grieco, D.L., Junhasavsaidkul, D., Rittayamai, N., Soliman, I., Sklar, M.C., Rauco, M., Ferguson, N.D., Fan, E., Richard, J.C.M.C.M., Brochard, L., 2020. Potential for lung recruitment estimated by the recruitment-to-inflation ratio during acute respiratory distress syndrome: a clinical trial. Am. J. Respir. Crit. Care Med. 201, 178–187. https://doi.org/10.1164/rccm.202102-3340OC.

Dantzker, D.R., Brook, C.J., Dehart, P., Lynch, J.P., Weg, J.G., 1979. Ventilation-perfusion distributions in the adult respiratory distress syndrome. Am. Rev. Respir. Dis. 120, 1039–1052. https://doi.org/10.1164/arrd.1979.120.5.1039.

Gattinoni, L., Cairoi, P., Cressoni, M., Chiumello, D., Ranieri, V.M., Quintel, M., Russo, S., Patroniti, N., Cornejo, R., Bugedo, G., 2006. Lung recruitment in patients with the acute respiratory distress syndrome. N. Engl. J. Med. 354, 1775-1786. https://doi.org/10.1056/NEJMo052052.

Gattinoni, L., Cairoi, D., Cairoi, P., Busana, M., Romitti, F., Brazzi, L., Camporota, L., 2020. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. 46, 1099–1102. https://doi.org/10.1007/s00134-020-06013-2.

Grasselli, G., Tonetti, T., Protti, A., Langer, T., Girardis, M., Bellani, G., Laffey, J., Antonelli, M., Sciaraffio, V., Zanella, A., Micucci, A., Benini, A., Scardoglio, A.M., Malar, A., Castelli, A., Colocuello, A., Micucci, A., Pesenti, A., Sala, A., Alborgetti, A., Antonini, B., Capra, C., Troiano, C., Rosi, C., Raddizzani, D., Chiumello, D., Coppini, B., Guzzon, D., Costantini, E., Malpetti, E., Zoia, E., Catena, E., Agosto, E., Barbera, E., Beretta, E., Boselli, E., Storti, E., Harizay, F., Della Mura, F., Lorini, F.L., Donato Sugiura, F., Marino, F., Mojoli, F., Rasulo, F., Grasselli, G., Casella, G., De Filippo, G., Castelli, G., Aldegheghi, G., Gallolio, G., Lotti, G., Albano, G., Landoni, G., Marino, G., Vitale, G., Battista Perego, G., Donati, G., Citerio, G., Friti, G., Natalini, G., Merli, G., Sforzini, L., Bianciardi, L., Carnevalle, L., Grazzioli, G., Caboni, M., Gueretti, L., Salvi, L., Dei Poli, M., Galletti, M., Gemma, M., Ranucci, M., Riccio, M., Borelli, M., Zambon, M., Subert, M., Ceccon, M., Mazzoni, M.G., Raimondi, M., Pasigada, M., Belliato, M., Bronzini, N., Larronco, N., Petracchi, N., Belgioni, N., Tagliabue, F., Cortellazzi, P., Gnesin, P., Grossou, P., Gritt, P., Perazzo, P., Severignini, P., Rubaggi, P., Sebastiano, P., Covello, R.D., Fernandez-Olmos, R., Fumagalli, R., Krin, R., Rona, R., Valacchi, R., Cattaneo, S., Colombo, S., Cirri, S., Bonazzi, S., Greco, S., Mutini, S., Langer, T., Alaimo, V., Wu, U., 2020b. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region. JAMA 24, 122. https://doi.org/10.1001/jama.2020.5394.

Grieco, D.L., Chen, L., Dres, M., Brochard, L., 2017. Should we use driving pressure to set tidal volume? Curr. Opin. Crit. Care Med. 23, 38–44. https://doi.org/10.1097/MCC.0000000000000377.

Grieco, D.L., Bongiovanni, F., Chen, L., Menga, L.S., Curuli, S.L., Piantaud, G., Carelli, S., Michi, T., Torrini, F., Lombardi, G., Anzellotti, G.M., De Pascale, G., Urbani, A., Boci, M.G., Tanzarella, E.S., Bello, G., Dell’Anna, A.M., Maggiore, S.M., Brochard, L., Antonelli, M., 2020. Respiratory physiology of COVID-19-induced respiratory failure compared to ARDS of other etiologies. Crit. Care 24, 529. https://doi.org/10.1186/s13054-020-02593-2.

Haudebourg, A.-F., Perier, F., Tuffet, S., de Prost, N., Razazi, K., Mekontso Dessap, A., Carteux, G., 2020. Respiratory mechanics of COVID-19 versus non-COVID-19-associated acute respiratory distress syndrome. Am. J. Respir. Crit. Care Med. 202, 287–296. https://doi.org/10.1164/rccm.202004-1226E.

Langer, T., Brioni, M., Guzzardella, A., Calori, E., Brioni, C., Castelli, G., Dalla Corte, F., De Robertis, E., Favaro, M., Forastier, A., Forlini, C., Girardis, M., Grieco, D.L., Mirabella, L., Negro, N., Tavolati, P., Protti, A., Rona, R., Tardini, F., Tonetti, T., Zanoni, F., Antonelli, M., Friti, G., Ranieri, M., Pesenti, A., Fumagalli, R., Grasselli, G., Benelli, A., Bove, T., Galligari, P., Coloretti, L., Colocuello, A., Costantini, F., Fanelli, V., Galliggi, G., Longhini, F., Mariani, F., Mascarello, A., Menga, L., Ottaviani, L., Pesci, A., Pezzi, A., Servillo, G., Severinghini, P., Spadaro, S., Zambelli, V., 2021. Prone position in intubated, mechanically ventilated patients with COVID-19: a multi-centric study of more than 1000 patients. Crit. Care 25, 1–11. https://doi.org/10.1186/s13054-021-03552-2.

Mekontso Dessap, A., Charron, C., Devaquet, J., Aboab, J., Jardin, F., Brochard, L., Vieillard-Baron, A., 2009. Impact of acute hypercapnia and augmented positive end-expiratory pressure on right ventricle function in severe acute respiratory distress syndrome. Intensive Care Med. 35, 1850–1858. https://doi.org/10.1007/s00134-009-1569-2.

Pelosi, P., Tubiolo, D., Mascheroni, D., Vicardi, P., Crotti, S., Valenza, F., Gattinoni, L., 1998. Effects of the prone position on respiratory mechanics and gas exchange during acute lung injury. Am. J. Respir. Crit. Care Med. 157, 397–393. https://doi.org/10.1164/ajrccm.157.2.97.04023.

Santamarina, M.G., Boisier, D., Contreras, B., Baque, M., Velpachio, R., Beddings, L., 2020. COVID-19: a hypothesis regarding the ventilation-perfusion mismatch. Crit. Care 24, 396. https://doi.org/10.1186/s13054-020-01325-9.

Spinelli, E., Grieco, D.L., Mauri, T., 2019. A personalized approach to the acute respiratory distress syndrome: recent advances and future challenges. J. Thorac. Dis. 11, 5619–5625. https://doi.org/10.21037/jtd.2019.11.61.