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Positive end-expiratory pressure in COVID-19 acute respiratory distress syndrome: the heterogeneous effects

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Abstract

Background: We hypothesized that as CARDS may present different pathophysiological features than classic ARDS, the application of high levels of end-expiratory pressure is questionable. Our first aim was to investigate the effects of 5–15 cmH₂O of PEEP on partitioned respiratory mechanics, gas exchange and dead space; secondly, we investigated whether respiratory system compliance and severity of hypoxemia could affect the response to PEEP on partitioned respiratory mechanics, gas exchange and dead space, dividing the population according to the median value of respiratory system compliance and oxygenation. Thirdly, we explored the effects of an additional PEEP selected according to the Empirical PEEP-FiO₂ table of the EPVent-2 study on partitioned respiratory mechanics and gas exchange in a subgroup of patients.

Methods: Sixty-one paralyzed mechanically ventilated patients with a confirmed diagnosis of SARS-CoV-2 were enrolled (age 60 [54–67] years, PaO₂/FiO₂ 113 [79–158] mmHg and PEEP 10 [10–10] cmH₂O). Keeping constant tidal volume, respiratory rate and oxygen fraction, two PEEP levels (5 and 15 cmH₂O) were selected. In a subgroup of patients an additional PEEP level was applied according to an Empirical PEEP-FiO₂ table (empirical PEEP). At each PEEP level gas exchange, partitioned lung mechanics and hemodynamic were collected.

Results: At 15 cmH₂O of PEEP the lung elastance, lung stress and mechanical power were higher compared to 5 cmH₂O. The PaO₂/FiO₂, arterial carbon dioxide and ventilatory ratio increased at 15 cmH₂O of PEEP. The arterial–venous oxygen difference and central venous saturation were higher at 15 cmH₂O of PEEP. Both the mechanics and gas exchange variables significantly increased although with high heterogeneity. By increasing the PEEP from 5 to 15 cmH₂O, the changes in partitioned respiratory mechanics and mechanical power were not related to hypoxemia or respiratory compliance. The empirical PEEP was 18 ± 1 cmH₂O. The empirical PEEP significantly increased the PaO₂/FiO₂ but also driving pressure, lung elastance, lung stress and mechanical power compared to 15 cmH₂O of PEEP.

Conclusions: In COVID-19 ARDS during the early phase the effects of raising PEEP are highly variable and cannot easily be predicted by respiratory system characteristics, because of the heterogeneity of the disease.

Keywords: SARS-CoV-2, COVID-19, Respiratory distress syndrome, Respiratory mechanics, Ventilator-induced lung injury

Background

The infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is characterized by an acute hypoxemic respiratory failure ranging from a mild to a

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severe form requiring intensive care admission and invasive mechanical ventilation in up to 30% of the severe forms of the disease [1, 2]. Based on the available body of evidence in order to limit the ventilator induced lung injury (VILI), not-related-to-COVID-19-ARDS patients are currently managed by applying low tidal volume without overcoming an inspiratory plateau pressure of 30 cmH₂O and moderate–high PEEP levels in the moderate–severe forms [3–5]. However, it has also been shown that among ARDS patients similar PEEP levels should not be used, but an individualization is required because the response to PEEP differs according to the respiratory mechanics, hemodynamic, lung recruitability and shunt. Inappropriately too high PEEP levels might promote lung overstress, increase in alveolar dead space and hemodynamic impairment amplifying the VILI [6, 7].

At the present time, no randomized clinical trials which examined the effect of PEEP in COVID-19 ARDS patients (CARDS) have been published [8]. The surviving sepsis campaign on the management of CARDS recommended a higher PEEP strategy rather than lower PEEP strategy [9]. A subsequent consensus of an international panel of experts did not reach any agreement on the PEEP level, suggesting that PEEP should be titrated according to a PEEP/FiO₂ table or to obtain the best respiratory compliance or the lowest driving pressure [10]. In a large extensive review of the literature the mean applied PEEP level was between 10 and 16 cmH₂O [8]. However, CARDS patients may present different characteristics from the ARDS, especially in the early phase [11]. CARDS patients may show a discrepancy between a relatively high respiratory system compliance, higher amount of lung gas volume and severity of hypoxemia [11–13]. Lung autopsy in patients who died from CARDS showed a diffuse alveolar damage with significant endotheliitis and microthrombi in the pulmonary vessels [13–16]. In particular, the alteration of perfusion into the lung could be due to an alteration in the hypoxic vasoconstriction (hyperperfusion in the poorly ventilated lung regions) and to a lower perfusion in the aerated lung regions rather than a lung collapse [16]. Consequently, if the vascular derangement is the major mechanism related to hypoxemia, the use of moderate–high PEEP levels is questionable.

Consequently, we hypothesized that as CARDS may present different pathophysiological features than classic ARDS, the application of high levels of end-expiratory pressure is questionable.

Our first aim was to investigate the effects of 5–15 cmH₂O of PEEP on partitioned respiratory mechanics, gas exchange and dead space; secondly, we investigated whether respiratory system compliance and severity of hypoxemia could affect the response to PEEP on partitioned respiratory mechanics, gas exchange and dead

space, dividing the population according to the median value of respiratory system compliance and oxygenation. Thirdly, we explored the effects of an additional PEEP selected according to the Empirical PEEP-FiO₂ table of the EPVent-2 study on partitioned respiratory mechanics and gas exchange in a subgroup of patients.

Methods

Study population

Sixty-one mechanically ventilated patients with a confirmed diagnosis of SARS-CoV-2 admitted to the general intensive care of the ASST Santi Paolo Carlo, Milan, Italy, were enrolled. Inclusion criteria were a laboratory confirmation of SARS-CoV-2 infection based on positive reverse transcriptase–polymerase chain reaction (RT-PCR) assay and diagnosis of ARDS, the day of the study. Exclusion criteria were the presence of barotrauma, the history of severe chronic obstructive pulmonary disease and the hemodynamic instability.

The study was approved by the local ethical committee (Comitato Etico Milano Area I; 2020/ST/095) and informed consent was obtained according to Italian regulations.

Study protocol

This was an observational study in which two levels of PEEP were tested.

A lung CT scan was performed during an end-expiratory pressure at 5 cmH₂O of PEEP.

All patients deeply sedated and paralyzed were ventilated in volume control with a tidal volume of 6–8 ml/kg of predicted body weight. Respiratory rate and inspiratory oxygen fraction were selected to maintain a pH and an arterial saturation between 7.34 and 7.44 and 88 and 95%, respectively. A PEEP level of 10 cmH₂O was clinically set at the beginning in all the patients during the stabilization period (60 min).

Subsequently, a recruitment maneuver was applied in pressure control ventilation with a PEEP of 5 cmH₂O to reach 45 cmH₂O of inspiratory plateau pressure with a respiratory rate of 10 for two minutes [17]. Keeping constant the tidal volume, respiratory rate and oxygen fraction, two PEEP levels (5 and 15 cmH₂O) were selected. Measurements are collected after 20 min of stabilization. The patients underwent the PEEP test in stable hemodynamic conditions. In addition, in a subgroup of 29 patients, the PEEP was adjusted according to the table named Empirical PEEP-FiO₂ of the EPVent-2 study [18]. The selected PEEP was called the “Empirical PEEP,” and for safety reason it was titrated to limit a maximum of 35 cmH₂O of inspiratory plateau airway pressure (Additional file 1: Fig. 1S).

Data collection

Twenty minutes after the application of the selected PEEP arterial/venous blood gas, lung mechanics and hemodynamic were collected. An end-inspiratory and end-expiratory pause were performed to measure the airway and esophageal pressure changes.

Gas exchange, respiratory mechanics and lung CT data

In order to measure the esophageal pressure, a radio-opaque balloon catheter (SmartCath Bicore, USA) was positioned in the lowest part of the esophagus and connected to a pressure transducer. The esophageal catheter was inflated of air with 1.5 mL and introduced transorally to reach the stomach at a depth between 50 and 55 cm from the mouth [19]. The intragastric position was confirmed by a rise in intra-abdominal pressure following external manual epigastric compression. Then, it was retracted into the esophagus (i.e., confirmed by the presence of cardiac artifacts in the pressure tracing and by the difference in the absolute pressure) at a distance between 35 and 40 cm from the mouth [19].

During an end-expiratory occlusion by compressing the thorax, the concordant changes of airway and esophageal pressure were verified to check the correct position of the balloon. The amount of gas in the balloon was periodically checked throughout the experiment.

The ventilatory ratio and the estimated physiological dead space were computed according to classic equations (See Additional File 1). The right-to-left intrapulmonary shunt was calculated accordingly to the venous admixture equation, using the blood gas values obtained from the central venous catheter as a surrogate of the mixed venous blood values [20].

The respiratory system, lung, chest wall elastance and lung stress were computed according to the standard formulas (see Additional File 1).

The mechanical power was calculated based on a mathematical simplification of the original mechanical power for volume control-ventilated patients [21]:

$$MP = 0.098 * \text{Respiratory rate} * \text{tidal volume} [\text{Peak airway Pressure} - (\text{Plateau airway Pressure} - \text{PEEP}) / 2]$$

The mechanical power was normalized to the respiratory system compliance [22].

The total lung weight, gas volume and the proportions of the different compartments (not inflated, poorly inflated, well inflated and overinflated) were computed with dedicated software (Maluna) [17].

Statistical analysis

Continuous data are presented as mean and standard deviation or median and interquartile range, as appropriate, while categorical data are reported as frequencies and percentage. A One-way ANOVA or Friedman test for repeated measure among the levels of PEEP was used to account for the repeated measures design; in case of statistical significance, Holm–Sidak test or Tukey’s test were used, respectively. Characteristics of the patients as well as the differences in respiratory mechanics, gas exchange between the two groups “high PaO₂/FiO₂” and “low PaO₂/FiO₂” or between “high Compliance” or “low Compliance” were compared by the Student’s t-test or Wilcoxon–Mann–Whitney rank sum test, as appropriate. The chi-square test or Fisher’s exact test of independence to analyze for frequency count. A *p* value of 0.05 or less was considered statistically significant. The statistical analysis was performed with SigmaPlot 11.0 (Systat Software, San Jose, CA) and RStudio (R Foundation for Statistical Computing, Vienna, Austria).

Results

The main characteristics of the patients are presented in Additional file 1: Table 1S. The days between the onset of symptoms and hospital admission were 6 [5–8]. The median PaO₂/FiO₂ at baseline was 113 [79–158] mmHg (15.1 [10.5–21.1] kPa). Thirty-eight patients (62%) and 19 patients (31%) presented a severe and moderate form of CARDS. The mean lung gas volume and weight were 1441 [923–2235] mL and 1348 [946–1647] g, respectively; the amount of not aerated tissue was 10.7 [3.1–19.1] % of the total lung weight (Additional file 1: Table 1S).

Response to 5–15 cmH₂O of PEEP on partitioned respiratory mechanics, gas exchange and dead space

In Table 1 the data of the respiratory mechanics and gas exchange at 5 and 15 cmH₂O of PEEP are presented. At 15 cmH₂O of PEEP the lung elastance, lung stress and mechanical power were significantly higher compared to 5 cmH₂O. Although the airway plateau pressure was

significantly higher at 15 cmH₂O, the driving pressure and elastance of respiratory system increased but did not reach statistical significance (Fig. 1; Additional file 1: Fig. 2S).

Concerning gas exchange, the PaO₂/FiO₂, arterial carbon dioxide and ventilatory ratio significantly increased

Table 1 Respiratory mechanics and gas exchange within 5 and 15 cmH₂O of PEEP

Variables	PEEP 5 61 patients	PEEP 15 61 patients	p
Plateau pressure, cmH ₂ O	17 ± 3	28 ± 3	<0.001
Driving pressure, cmH ₂ O	12 ± 3	13 ± 3	0.071
Respiratory system elastance, cmH ₂ O/L	23 [19–27]	24 [21–31]	0.093
Lung elastance, cmH ₂ O/L	18 [15–22]	19 [17–25]	0.049
Chest wall elastance, cmH ₂ O/L	5 [3–6]	4 [3–6]	0.845
Lung stress, cmH ₂ O	13.1 ± 3.1	22.3 ± 4.0	<0.001
Mechanical power, J/min	16.7 ± 5.7	26.1 ± 6.4	<0.001
Mechanical Power_Compliance _{rs} , J/min/(mL/cmH ₂ O)	0.36 [0.27–0.50]	0.61 [0.51–0.77]	<0.001
PaO ₂ , mmHg	63 [55–76]	84 [74–99]	<0.001
PaO ₂ /FiO ₂ , mmHg	82 [66–138]	127 [90–184]	<0.001
Right-to-left shunt, %	47 ± 15	35 ± 12	<0.001
PvO ₂ , mmHg	42 ± 7	47 ± 7	<0.001
ScvO ₂ , %	74 ± 8	79 ± 6	<0.001
C _{a-v} O ₂ , mL	2.8 [2.3–3.2]	3.0 [2.4–3.4]	0.024
PaCO ₂ , mmHg	48 ± 9	50 ± 9	<0.001
Ventilatory ratio	1.66 ± 0.39	1.74 ± 0.37	0.002
Estimated physiological dead space	0.50 [0.43–0.58]	0.52 [0.42–0.60]	<0.001

Paired T-test or Wilcoxon–Mann–Whitney test for repeated measures were performed, as appropriate. Tidal volume and respiratory rate were unchanged between the two PEEP levels. C_{a-v}O₂: arterial–venous oxygen content difference; Compliance_{rs}: respiratory system compliance; ScvO₂ central oxygen venous saturation; PvO₂ mixed venous oxygen tension

at 15 cmH₂O of PEEP. The arterial–venous oxygen difference and central venous saturation were significantly higher at 15 cmH₂O of PEEP. The shunt significantly decreased at 15 cmH₂O of PEEP. Increasing PEEP from 5 to 15 cmH₂O the mechanics and gas exchange variables that significantly increased showed high heterogeneity.

Response to 5–15 cmH₂O of PEEP according to the compliance of respiratory system and severity of hypoxemia

Considering the median of respiratory compliance of the whole population (44 ml/cmH₂O) to separate the population in a high and a low compliance group, the first group had a higher lung gas volume and well inflated lung tissue (Additional file 1: Table 2S; Fig. 3S). The oxygenation and ventilatory ratio were not different (Additional file 1: Table 2S).

By increasing the PEEP from 5 to 15 cmH₂O, the changes in the partitioned respiratory system elastance and gas exchange were similar between the two groups (Table 2, Additional file 1: Fig. 5S).

Furthermore, we also divided the whole population according to the median of the PaO₂/FiO₂ (81.8 mmHg or 10.9 kPa), in high and low PaO₂/FiO₂ groups. The two groups presented similar lung gas volume, not inflated tissue and partitioned respiratory mechanics (Additional file 1: Table 3S; Fig. 4S). By increasing the PEEP from 5 to 15 cmH₂O, the changes in partitioned respiratory

mechanics and mechanical power were similar (Table 3, Additional file 1: Fig. 6S).

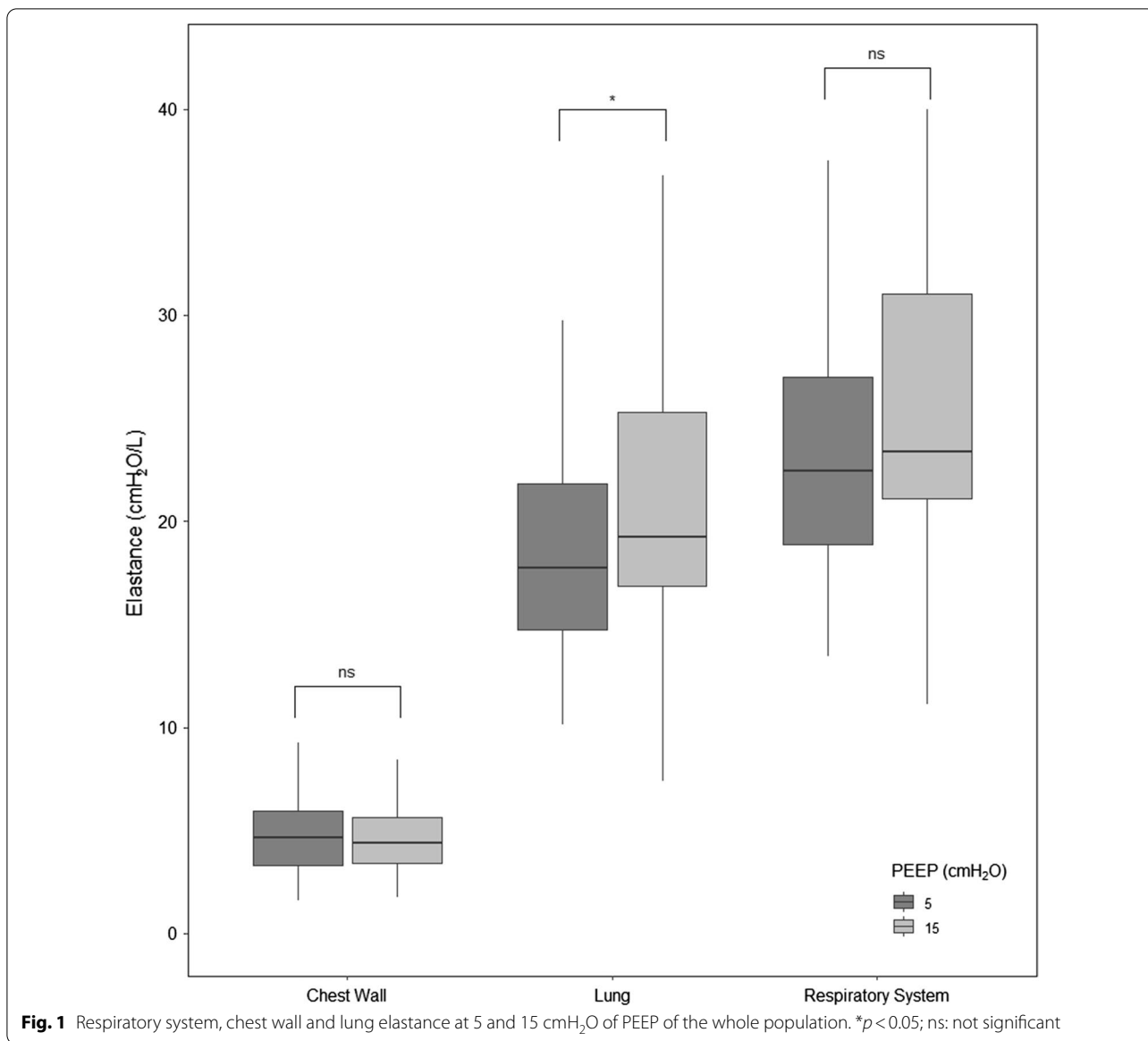
Response to Empirical PEEP on partitioned respiratory mechanics, gas exchange and dead space

In a subgroup of 29 patients the Empirical PEEP has been selected according to the PEEP/FiO₂ table. The Empirical PEEP was 18 ± 1 cmH₂O. The Empirical PEEP significantly increased the driving pressure, elastance, lung stress and mechanical power compared to 15 cmH₂O of PEEP (Additional file 1: Table 4S; Fig. 7S). At the Empirical PEEP the PaO₂/FiO₂ was higher compared to 15 cmH₂O of PEEP, while carbon dioxide and ventilatory ratio were similar.

Discussion

The main findings of this study evaluating different PEEP levels, with constant tidal volume, were: (1) 15 cmH₂O of PEEP significantly increased the ventilatory ratio, lung elastance and mechanical power although with heterogeneous responses, (2) the arterial oxygenation increased by increasing the PEEP, (3) the compliance of the respiratory system and the level of hypoxemia at baseline did not affect the PEEP response and (4) the PEEP suggested by the PEEP/FiO₂ table was higher than 15 cmH₂O.

Most mechanically ventilated CARDS patients fulfill the criteria of ARDS according to the Berlin definition [23, 24]. Typically, ARDS is characterized by an



inflammatory pulmonary edema, shunt related hypoxemia and reduction both in lung gas volume and in the respiratory compliance [6]. Higher PEEP levels, recruitment maneuvers and prone positioning are suggested to recruit the lung [4, 7]. However, COVID-19 is a systemic disease which besides affecting mainly the lung, can also damage the vascular endothelium [13, 17]. It has been reported an activation of the coagulation cascade with an associated micro–macro thrombosis in the lung. It has also been found the presence of vessels enlargement in the ground glass opacities, suggesting the presence of a thrombotic inflammatory process [16]. The available data clearly indicate that CARDS can present heterogeneous characteristics with a relatively high respiratory

system compliance [11, 12, 25–27]. Our group proposed the presence of two phenotypes in CARDS based on lung mechanics properties, type L (low elastance) and type H (high elastance) [28, 29]. In the present study our population had a median of 2 [2] days of mechanical ventilation since intubation and the PEEP trial, presented a median compliance of respiratory system of 44 ml/cmH₂O. Similar data were also reported by other groups [25, 30, 31]. In a recent review, the compliance values at 1 SD above the mean or the 75th percentile > 50 ml/cmH₂O were reported in 43% of the studies [8]. Similarly, the lung gas volume computed by CT was also considerable high, a median of 2952 [2038–3617] mL, contrary to previous

Table 2 Changes in respiratory mechanics and gas exchange at 5 and 15 cmH₂O of PEEP between high and low respiratory system compliance group

Variables	Low C _{rs} < 44 mL/cmH ₂ O 30 patients	High C _{rs} ≥ 44 mL/cmH ₂ O 31 patients	p
Δ ₁₅₋₅ Plateau pressure, cmH ₂ O	10 [7–12]	11 [10–13]	0.042
Δ ₁₅₋₅ Driving pressure, cmH ₂ O	0 [– 3 to 2]	1 [0–3]	0.042
Δ ₁₅₋₅ Respiratory system elastance, cmH ₂ O/L	– 1 [– 5 to 4]	2 [0–6]	0.057
Δ ₁₅₋₅ Lung elastance, cmH ₂ O/L	2 [– 2 to 5]	2 [0–5]	0.286
Δ ₁₅₋₅ Chest wall elastance, cmH ₂ O/L	0 [– 2 to 2]	0 [– 1 to 0]	0.305
Δ ₁₅₋₅ Lung stress, cmH ₂ O	9 [6–11]	9 [8–12]	0.256
Δ ₁₅₋₅ Mechanical power, J/min	9 [8–12]	9 [8–11]	0.866
Δ ₁₅₋₅ Mechanical Power_Compliance _{rs} , J/min/(mL/cmH ₂ O)	0.26 [0.12–0.40]	0.23 [0.16–0.35]	0.656
Δ ₁₅₋₅ PaO ₂ , mmHg	20 [13–38]	20 [6–30]	0.336
Δ ₁₅₋₅ PaO ₂ /FiO ₂ , mmHg	28 [16–51]	30 [10–50]	0.657
Δ ₁₅₋₅ Right-to-left shunt, %	– 12 [– 23 to – 1]	– 9 [– 18 to – 5]	0.710
Δ ₁₅₋₅ PvO ₂ , mmHg	4.0 [2.3–8.8]	2.0 [1.0–8.1]	0.219
Δ ₁₅₋₅ ScvO ₂ , %	5.5 [1.0–10.8]	2.5 [0.0–8.1]	0.184
Δ ₁₅₋₅ C _{a-v} O ₂ , mL	1.0 [0.3–1.7]	0.6 [0.2–1.3]	0.331
Δ ₁₅₋₅ PaCO ₂ , mmHg	1 [– 1 to 3]	2 [1–4]	0.226
Δ ₁₅₋₅ Ventilatory ratio	0.04 [– 0.10 to 0.10]	0.08 [0.02–0.20]	0.119
Δ ₁₅₋₅ Estimated physiological dead space	0.01 [– 0.01 to 0.03]	0.02 [0.01–0.05]	0.119

T-test or Wilcoxon–Mann–Whitney test were performed, as appropriate. Δ₁₅₋₅: difference between 15 and 5 cmH₂O of PEEP; C_{a-v}O₂: arterial–venous oxygen content difference; Compliance_{rs}: respiratory system compliance; ScvO₂ central oxygen venous saturation; PvO₂ mixed venous oxygen tension

Table 3 Changes in respiratory mechanics and gas exchange at 5 and 15 cmH₂O of PEEP between high and low PaO₂/FiO₂ group

Variables	Low PaO ₂ /FiO ₂ < 81.8 31 patients	High PaO ₂ /FiO ₂ ≥ 81.8 30 patients	p
Δ ₁₅₋₅ Plateau pressure, cmH ₂ O	8 [10–11]	11 [10–13]	0.147
Δ ₁₅₋₅ Driving pressure, cmH ₂ O	0 [– 2 to 1]	1 [0–3]	0.147
Δ ₁₅₋₅ Respiratory system elastance, cmH ₂ O/L	0 [– 3 to 3]	3 [0–6]	0.126
Δ ₁₅₋₅ Lung elastance, cmH ₂ O/L	2 [– 2 to 4]	3 [1–7]	0.257
Δ ₁₅₋₅ Chest wall elastance, cmH ₂ O/L	0 [– 2 to 1]	0 [– 2 to 2]	0.373
Δ ₁₅₋₅ Lung stress, cmH ₂ O	9 [7–11]	9 [8–13]	0.534
Δ ₁₅₋₅ Mechanical power, J/min	9 [8–11]	10 [9–11]	0.351
Δ ₁₅₋₅ Mechanical Power_Compliance _{rs} , J/min/(mL/cmH ₂ O)	0.21 [0.12–0.34]	0.30 [0.17–0.37]	0.436
Δ ₁₅₋₅ PaO ₂ , mmHg	26 [16–38]	16 [4–23]	0.012
Δ ₁₅₋₅ PaO ₂ /FiO ₂ , mmHg	31 [16–55]	28 [9–42]	0.212
Δ ₁₅₋₅ Right-to-left shunt, %	– 16 [– 26 to – 10]	0 [– 11 to 0]	< 0.001
Δ ₁₅₋₅ PvO ₂ , mmHg	3 [2–11]	1 [0–2]	< 0.001
Δ ₁₅₋₅ ScvO ₂ , %	8.5 [4.4–13.4]	0.6 [– 1 to 3]	< 0.001
Δ ₁₅₋₅ C _{a-v} O ₂ , mL	1.3 [0.9–1.8]	0.4 [0.0–0.6]	< 0.001
Δ ₁₅₋₅ PaCO ₂ , mmHg	1 [– 2 to 3]	2 [1–5]	0.110
Δ ₁₅₋₅ Ventilatory ratio	0.04 [– 0.09 to 0.10]	0.08 [– 0.02 to 0.19]	0.065
Δ ₁₅₋₅ Estimated physiological dead space	0.01 [– 0.02 to 0.03]	0.02 [0.01–0.05]	0.070

T-test or Wilcoxon–Mann–Whitney test were performed, as appropriate. Δ₁₅₋₅: difference between 15 and 5 cmH₂O of PEEP; C_{a-v}O₂: arterial–venous oxygen content difference; Compliance_{rs}: respiratory system compliance; ScvO₂ central oxygen venous saturation; PvO₂ mixed venous oxygen tension

data on ARDS patients in which the lung gas volume (i.e., baby lung) was typically reduced [17, 32, 33].

In a recent review analyzing the available data about mechanical ventilation setting in CARDS, it was reported that PEEP values ranged from 9 to 16.5 cmH₂O [8]. The PEEP was selected mainly according to the change in oxygenation or to a PEEP/FiO₂ table [34, 35].

Response to 5–15 cmH₂O of PEEP on partitioned respiratory mechanics, gas exchange and dead space

In this study we choose to evaluate the effects of two different PEEP levels (5 and 15 cmH₂O) based on previous studies which defined as “low” and “moderate–high” PEEP [17, 36]. The higher PEEP levels significantly increased the oxygenation and reduced the alveolar shunt. However, at the same time, in the majority of patients the ventilatory ratio was higher indicating a less efficiently CO₂ clearance (i.e., higher dead space) as well as the respiratory system compliance decreased. Similar data was also found by Mauri et al. in a small group of CARDS (10 patients), in which 15 cmH₂O of PEEP was associated with a better oxygenation and higher arterial carbon dioxide [25]. In patients with ARDS it has been observed that increasing PEEP the arterial oxygenation increased by a reduction in the intrapulmonary shunt with also an increase in the dead space [37].

More importantly, in our patients the increase of PEEP significantly increased the arterial–venous difference in oxygenation and the central venous oxygenation.

Thus, the ameliorating in oxygenation at higher PEEP levels seems more related to the modification of the ventilation/perfusion ratio in the lung areas with low ventilation/perfusion rather than a lung recruitment (i.e., reopening of collapsed lung regions) [11]. The reduction in the alveolar shunt could also be due to a decrease in cardiac output by the higher levels of PEEP [37–39].

Although the plateau airway pressure and driving pressure are commonly used as surrogate of the VILI, the real distending force of the lung is the transpulmonary pressure [4, 40, 41]. The transpulmonary pressure computed by the esophageal balloon technique is closely related to the lung stress [41, 42]. Thus, in the present study we assessed both the lung elastance and the lung stress. The enrolled patients have a relatively normal chest wall elastance which contributes to the elastance of the respiratory system by approximately 20–30% [41]. By note, at higher PEEP levels the lung elastance and lung stress were significantly higher. In a previous small study, applying the electrical impedance tomography technique (EIT), higher PEEP levels were associated with higher lung elastance and to higher lung overdistension evaluated by EIT technique [43]. In addition to evaluate the overall effect of different levels of PEEP, we computed the

mechanical power which depends on the driving pressure, tidal volume, respiratory rate and PEEP. The respiratory rate and tidal volume did not change throughout the study; thus, the mechanical power resulted from the interaction of PEEP and driving pressure. By increasing PEEP, the mechanical power and the normalized mechanical power for the compliance of respiratory system (i.e., to take into account the size of the lung) were much higher compared to low PEEP level.

Response to 5–15 cmH₂O of PEEP according to the compliance of respiratory system and severity of hypoxemia

In ARDS patients several studies evaluated the possible factors associated with PEEP response [4, 6]. We found a comparable median response to PEEP in both patients with a low and high respiratory system compliance and with high and low PaO₂/FiO₂ in whom the oxygenation improved, the mechanical power significantly increased while the ventilatory ratio and respiratory mechanics, although deteriorating, showed high heterogeneity. Perier et al., comparing two CARDS subgroups based on the compliance of the respiratory system assessed at low PEEP level, found a similar behavior in terms of collapse, hyperdistention and oxygenation by applying a range of PEEP from 6 to 18 cmH₂O [44]. In our population, the more hypoxemic group, which seems to improve the oxygenation when PEEP was increased from 5 to 15 cmH₂O, showed the same quantitative radiological features at the CT scan at 5 cmH₂O compared with less hypoxemic group. This can partially explain that the changes in the partitioned respiratory system elastance and gas exchange were similar between the two groups. Similarly, the group with low and high respiratory system compliance presented the same amount of not and poorly inflated tissue, with similar changes in the partitioned respiratory system elastance and gas exchange between the two groups.

Response to Empirical PEEP on partitioned respiratory mechanics, gas exchange and dead space

In ARDS patients the use of PEEP-FiO₂ tables is a quite common approach in clinical practice mainly due to the greater ease of application [4]. Several PEEP-FiO₂ tables have been proposed over the decades [4, 6]. In two ARDS randomized clinical trials that compared a lower and higher PEEP-FiO₂ table, the arterial oxygenation increased with the higher PEEP table, suggesting a higher lung recruitment a better outcome [6]. In ARDS patients the PEEP-FiO₂ table was able to provide PEEP levels according to the lung recruitability [7]. In the present study applying a PEEP-FiO₂ combination table commonly suggested in ARDS, the proposed average PEEP level was 18 ± 1 cmH₂O. However, this Empirical PEEP

level was associated with a significantly higher oxygenation but to a worsening in ventilatory ratio and lung elastance compared to 15 cmH₂O. Tsolaki et al., applying the ARDS net protocol, according to the Surviving sepsis campaign, found that the suggested PEEP level was 18 cmH₂O instead of a mean level of 8 cmH₂O of PEEP, when the best combination of respiratory system compliance, CO₂ clearance and hemodynamic was used [45]. In a small study of 15 CARDS comparing the PEEP selected by the EIT technique to obtain to the best compromise between lung collapse and overdistension, with PEEP/FiO₂ table approach, the latter suggested higher PEEP (17 vs 12 cmH₂O) [46]. Thus, if we followed in CARDS the Empirical PEEP-FiO₂ table, significantly higher PEEP levels should have been applied in lungs with almost normal compliance with possible detrimental consequences.

This study has several strengths: Firstly, it is the first study which computed the lung compliance and mechanical power during the change of PEEP; secondly, it evaluated two PEEP levels (low and moderate/high) compared to an Empirical PEEP-FiO₂ table, which is suggested in ARDS patients.

Limitations

The possible limitations of this study were the absence of any data regarding the computation of lung recruitability at 15 cmH₂O of PEEP and regarding the changes of cardiac output at the different PEEP levels.

Conclusions

In conclusion, the main finding of this study evaluating different PEEP levels with constant tidal volume was that the effects of raising PEEP are highly variable among CARDS patients and cannot easily be predicted by respiratory system characteristics, because of the heterogeneity of the disease, including with respect to respiratory system compliance and hypoxia that is mainly due to low V/Q respond less than to true shunt. Moreover, the PEEP adjusted according to the Empirical PEEP-FiO₂ table resulted in an unnecessary much higher PEEP levels possibly which was not related to the pathophysiology of CARDS patients. Moderate PEEP levels are able to redistribute the pulmonary blood flow, ameliorate oxygenation and avoid the lung over stress and strain and the impairment of cardiac function with a higher need of fluids and vasopressor. Thus, in CARDS tailoring PEEP based on a “PEEP test,” represents an invaluable option to set a protective lung ventilation and prevent further damage to the lungs.

Abbreviations

ARDS: Acute respiratory distress syndrome; CARDS: COVID19 ARDS; COVID19: Coronavirus disease 2019; FiO₂: Fraction of inspired oxygen; EIT: Electrical impedance tomography technique; PEEP: Positive end-expiratory pressure; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13054-021-03839-4>.

Additional file 1. Respiratory mechanics and physiological variables formulas; study protocol flow-chart; baseline characteristics table; additional data about PEEP 5-15cmH₂O comparison; boxplot and linear regression graphs.

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Authors' contributions

DC conceived and presented the idea, designed the study, interpreted the data and drafted and revised the paper; MB monitored data collection and revised the draft paper; TP monitored data collection and performed the statistical analysis; PF interpreted the data and revised the draft paper; GFSP revised the draft paper; GZ monitored data collection and revised the draft paper; SC designed the study, performed the statistical analysis, interpreted the data and revised the draft paper. All authors read and approved the final manuscript.

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Availability of data and materials

The dataset used in writing this manuscript are available from the corresponding author after reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the local ethical committee (Comitato Etico Milano Area I; 2020/ST/095) and informed consent was obtained according to Italian regulations;

Consent for publication

All the authors expressed their consent to publication on Critical Care.

Competing interests

The authors declare there are no competing interests.

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References

- Attaway AH, Scheraga RG, Bhimraj A, Biehl M, Hatipoğlu U. Severe covid-19 pneumonia: pathogenesis and clinical management. *BMJ Br Med J*. 2021;372:m436.
- Radovanovic D, Coppola S, Franceschi E, Gervasoni F, Duscio E, Alberto D, et al. Mortality and clinical outcomes in patients with COVID-19 pneumonia treated with non-invasive respiratory support: a rapid review. *J Crit Care*. 2021;65:1–8.
- Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. *New Engl J Med*. 2017;377:562–72.
- Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, et al. An official American Thoracic Society/European Society of intensive care medicine/society of critical care medicine clinical practice guideline: Mechanical ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2017;195(9):1253–63.
- Chiumello D, Brochard L, Marini JJ, Slutsky AS, Mancebo J, Ranieri VM, et al. Respiratory support in patients with acute respiratory distress syndrome: an expert opinion. *Crit Care*. 2017;21(1):240.
- Sahetya SK, Goligher EC, Brower RG. Fifty years in research in ARDS: setting positive end-expiratory pressure in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2017;195(11):1429–38.
- Chiumello D, Cressoni M, Carlesso E, Caspani ML, Marino A, Gallazzi E, et al. Bedside selection of positive end-expiratory pressure in mild, moderate, and severe acute respiratory distress syndrome. *Crit Care Med*. 2014;42(2):252–64.
- Kallet RH. The year in review: mechanical ventilation during the first year of the Covid-19 pandemic. *Respir Care*. 2021;respcare.09257.
- Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Medicine*. Springer Berlin Heidelberg; 2020.
- Nasa P, Azoulay E, Khanna AK, Jain R, Gupta S, Javeri Y, et al. Expert consensus statements for the management of COVID-19-related acute respiratory failure using a Delphi method. *Crit Care*. 2021;25(1):1–17.
- Chiumello D, Busana M, Coppola S, Romitti F, Formenti P, Bonifazi M, et al. Physiological and quantitative CT-scan characterization of COVID-19 and typical ARDS: a matched cohort study. *Intensive Care Med*. 2020;46(12):2187–96.
- Ball L, Robba C, Maiello L, Herrmann J, Gerard SE, Xin Y, et al. Computed tomography assessment of PEEP-induced alveolar recruitment in patients with severe COVID-19 pneumonia. *Crit Care*. 2021;25(1):1–10.
- Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJJ. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med*. 2020;383(2):120–8.
- Barton LM, Duval EJ, Stroberg E, Ghosh S. COVID-19 autopsies, Oklahoma, USA. *Am J Clin Pathol*. 2020;20:1–9.
- Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Correspondence Endothelial cell infection and endotheliitis in. *Lancet*. 2019;395(10234):1417–8.
- Santamarina MG, Boisier D, Contreras R, Baque M, Volpacchio M, Beddings I. COVID-19: a hypothesis regarding the ventilation-perfusion mismatch. *Crit Care*. 2020;24(1):4–7.
- Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med*. 2006;354(17):1775–86.
- Beitler JR, Sarge T, Banner-Goodspeed VM, Gong MN, Cook D, Novack V, et al. Effect of titrating positive end-expiratory pressure (PEEP) with an esophageal pressure-guided strategy vs an empirical high PEEP-F io 2 strategy on death and days free from mechanical ventilation among patients with acute respiratory distress syndrome: A. *JAMA J Am Med Assoc*. 2019;321(9):846–57.
- Chiumello D, Consonni D, Coppola S, Froio S, Crimella F. The occlusion tests and end-expiratory esophageal pressure: measurements and comparison in controlled and assisted ventilation. *Ann Intensive Care*. 2016;56:1–10.
- Radermacher P, Maggiore SM, Mercat A. Gas exchange in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2017;196(8):964–84.
- Gattinoni L, Tonetti T, Cressoni M, Cadringer P, Herrmann P, Moerer O, et al. Ventilator-related causes of lung injury: the mechanical power. *Intensive Care Med*. 2016;42(10):1567–75.
- Coppola S, Caccioppola A, Froio S, Formenti P, De Giorgis V, Galanti V, et al. Effect of mechanical power on intensive care mortality in ARDS patients. *Crit Care*. 2020;24(1):1–10.
- Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA J Am Med Assoc*. 2020;323(16):1574–81.
- Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;1–10.
- Mauri T, Spinelli E, Scotti E, Colussi G, Basile MC, Crotti S, et al. Potential for lung recruitment and ventilation-perfusion mismatch in patients with the acute respiratory distress syndrome from coronavirus disease 2019. *Crit Care Med*. 2020;48(8):1129–34.
- Beloncle FM, Pavlovsky B, Desprez C, Fage N, Olivier PY, Asfar P, et al. Recruitability and effect of PEEP in SARS-Cov-2-associated acute respiratory distress syndrome. *Ann Intensive Care*. 2020;10(1):55.
- Ball L, Robba C, Herrmann J, Gerard SE, Xin Y, Mandelli M, et al. Lung distribution of gas and blood volume in critically ill COVID-19 patients: a quantitative dual-energy computed tomography study. *Crit Care*. 2021;25(1):1–12.
- Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatment for different phenotypes? *Intensi*. 2020;46(4):1099–102.
- Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi SCD. COVID-19 Does not lead to a “typical” acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2020;201(10):1299–300.
- Grasselli G, Cattaneo E, Florio G, Ippolito M, Zanella A, Cortegiani A, et al. Mechanical ventilation parameters in critically ill COVID-19 patients: a scoping review. *Crit Care*. 2021;25(1):1–11.
- Haudebourg AF, Perier F, Tuffet S, De Prost N, Razazi K, Dessap AM, et al. Respiratory mechanics of COVID-19- versus Non-COVID-19-associated acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2020;202(2):287–90.
- Gattinoni L, Pesenti ABM. Relationships between lung computed tomographic density, gas exchange, and PEEP in acute respiratory failure. *Anesthesiology*. 1988;69(6):824–32.
- Malbouisson LM, Muller J-C, Constantin J-M, Lu Q, Puybasset L, Rouby J-J. Computed tomography assessment of positive end-expiratory pressure-induced alveolar recruitment in patients with acute respiratory distress syndrome [1] (multiple letters). *Am J Respir Crit Care Med*. 2002;165(4):551.
- Ziehr DR, Alladina J, Petri CR, Maley JH, Moskowitz A, Medoff BD, et al. Respiratory pathophysiology of mechanically ventilated patients with COVID-19: A cohort study. *Am J Respir Crit Care Med*. 2020;201(12):1560–4.
- Laverdure F, Delaporte A, Bouteau A, Genty T, Decailliot F, Stéphan F. Impact of initial respiratory compliance in ventilated patients with acute respiratory distress syndrome related to COVID-19. *Crit Care*. 2020;24(412):1–4.
- Caironi P, Cressoni M, Chiumello D, Ranieri M, Quintel M, Russo SG, et al. Lung opening and closing during ventilation of acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2010;181:578–86.
- Suter PM, Fairley B, Isenberg M. Optimum End-Expiratory airway pressure in patients with acute pulmonari failure. *N Engl J Med*. 1975;292(6):284–9.
- Barthélémy R, Beaucofé V, Bordier R, Collet M, Le Gall A, Hong A, et al. Haemodynamic impact of positive end-expiratory pressure in SARS-CoV-2 acute respiratory distress syndrome: oxygenation versus oxygen delivery. *Br J Anaesth*. 2021;126(2):e70–2.
- Dantzker DR, Lynch JP, Weg JG. Depression of cardiac output is a mechanism of shunt reduction in the therapy of acute respiratory failure. *Chest*. 1980;77(5):636–42.
- Amato M, Meade MO, Slutsky AS, Brochard L, Costa ELVC, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. *New Engl J Med J Med*. 2015;372(8):747–55.
- Chiumello D, Carlesso E, Cadringer P, Caironi P, Valenza F, Polli F, et al. Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2008;178(4):346–55.

42. Akoumianaki E, Maggiore SM, Valenza F, Bellani G, Jubran A, Loring SH, et al. The application of esophageal pressure measurement in patients with respiratory failure. *Am J Respir Crit Care Med.* 2014;189(5):520–31.
43. Bonny V, Janiak V, Spadaro S, Pinna A, Demoule A, Dres M. Correction to: Effect of PEEP decremental on respiratory mechanics, gas exchange, pulmonary regional ventilation, and hemodynamics in patients with SARS-Cov-2-associated Acute Respiratory Distress Syndrome. *Crit Care.* 2020;24(1):1–4.
44. Perier F, Tuffet S, Maraffi T, Alcalá G, Victor M, Haudebourg AF, et al. Electrical impedance tomography to titrate positive end-expiratory pressure in COVID-19 acute respiratory distress syndrome. *Crit Care.* 2020;24(1):1–9.
45. Tsolaki V, Siempos I, Magira E, Kokkoris S, Zakyntinos GE, Zakyntinos S. PEEP levels in COVID-19 pneumonia. *Crit Care.* 2020;24(1):1–2.
46. Sella N, Zarantonello F, Andreatta G, Gagliardi V, Boscolo A, Navalesi P. Positive end-expiratory pressure titration in COVID-19 acute respiratory failure: electrical impedance tomography vs. PEEP/FiO₂ tables. *Crit Care.* 2020;24(1):5–7.

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