

Effects of CPAP and FiO₂ on respiratory effort and lung stress in early COVID-19 pneumonia: a randomized, crossover study

Original

Effects of CPAP and FiO₂ on respiratory effort and lung stress in early COVID-19 pneumonia: a randomized, crossover study / Giosa, L., Collins, P.D., Sciolla, M., Cerrone, F., Di Blasi, S., Macri, M.M., Davicco, L., Laguzzi, A., Gorgonzola, F., Penso, R., Steinberg, I., Muraccini, M., Perboni, A., Russotto, V., Camporota, L., Bellani, G., Caironi, P.. - In: ANNALS OF INTENSIVE CARE. - ISSN 2110-5820. - 13:1(2023). [10.1186/s13613-023-01202-0]

Availability:

This version is available at: 11583/2993701 since: 2024-10-25T13:46:19Z

Publisher:

Springer Science and Business Media Deutschland GmbH

Published

DOI:10.1186/s13613-023-01202-0

Terms of use:

This article is made available under terms and conditions as specified in the corresponding bibliographic description in the repository

Publisher copyright


(Article begins on next page)

RESEARCH

Open Access



Effects of CPAP and FiO₂ on respiratory effort and lung stress in early COVID-19 pneumonia: a randomized, crossover study

Lorenzo Giosa^{1,2*} , Patrick Duncan Collins¹, Martina Sciolla³, Francesca Cerrone⁴, Salvatore Di Blasi⁵, Matteo Maria Macri⁵, Luca Davicco⁵, Andrea Laguzzi⁵, Fabiana Gorgonzola³, Roberto Penso⁵, Irene Steinberg^{6,7}, Massimo Muraccini⁶, Alberto Perboni³, Vincenzo Russotto^{5,8}, Luigi Camporota^{1,2}, Giacomo Bellani^{9,10} and Pietro Caironi^{5,8}

Abstract

Background In COVID-19 acute respiratory failure, the effects of CPAP and FiO₂ on respiratory effort and lung stress are unclear. We hypothesize that, in the compliant lungs of early Sars-CoV-2 pneumonia, the application of positive pressure through Helmet-CPAP may not decrease respiratory effort, and rather worsen lung stress and oxygenation when compared to higher FiO₂ delivered via oxygen masks.

Methods In this single-center (S.Luigi Gonzaga University-Hospital, Turin, Italy), randomized, crossover study, we included patients receiving Helmet-CPAP for early (< 48 h) COVID-19 pneumonia without additional cardiac or respiratory disease. Healthy subjects were included as controls. Participants were equipped with an esophageal catheter, a non-invasive cardiac output monitor, and an arterial catheter. The protocol consisted of a random sequence of non-rebreather mask (NRB), Helmet-CPAP (with variable positive pressure and FiO₂) and Venturi mask (FiO₂ 0.5), each delivered for 20 min. Study outcomes were changes in respiratory effort (esophageal swing), total lung stress (dynamic + static transpulmonary pressure), gas-exchange and hemodynamics.

Results We enrolled 28 COVID-19 patients and 7 healthy controls. In all patients, respiratory effort increased from NRB to Helmet-CPAP (5.0 ± 3.7 vs 8.3 ± 3.9 cmH₂O, p < 0.01). However, Helmet's pressure decreased by a comparable amount during inspiration (− 3.1 ± 1.0 cmH₂O, p = 0.16), therefore dynamic stress remained stable (p = 0.97). Changes in static and total lung stress from NRB to Helmet-CPAP were overall not significant (p = 0.07 and p = 0.09, respectively), but showed high interpatient variability, ranging from − 4.5 to + 6.1 cmH₂O, and from − 5.8 to + 5.7 cmH₂O, respectively. All findings were confirmed in healthy subjects, except for an increase in dynamic stress (p < 0.01). PaO₂ decreased from NRB to Helmet-CPAP with FiO₂ 0.5 (107 ± 55 vs 86 ± 30 mmHg, p < 0.01), irrespective of positive pressure levels (p = 0.64). Conversely, with Helmet's FiO₂ 0.9, PaO₂ increased (p < 0.01), but oxygen delivery remained stable (p = 0.48) as cardiac output decreased (p = 0.02). When PaO₂ fell below 60 mmHg with VM, respiratory effort increased proportionally (p < 0.01, r = 0.81).

Conclusions In early COVID-19 pneumonia, Helmet-CPAP increases respiratory effort without altering dynamic stress, while the effects upon static and total stress are variable, requiring individual assessment. Oxygen masks with higher FiO₂ provide better oxygenation with lower respiratory effort.

*Correspondence:

Lorenzo Giosa

lorenzo.giosa@gmail.com

Full list of author information is available at the end of the article



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

Trial registration Retrospectively registered (13-May-2021): [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/NCT04885517) (NCT04885517), <https://clinicaltrials.gov/ct2/show/NCT04885517>.

Keywords COVID-19, Respiratory failure, Helmet-CPAP, Non-rebreather mask, Venturi mask, Respiratory effort, Lung stress, Gas-exchange, Hemodynamics

Background

Randomized controlled trials have suggested that CPAP may reduce the rate of intubation in COVID-19, without affecting mortality or length of stay [1–4]. However, these studies did not assess the effects of CPAP on respiratory effort and lung stress, which may contribute to the progression of lung injury [5, 6].

Theoretically, CPAP has the potential to alleviate respiratory effort and lung stress in acute respiratory failure (ARF) [7, 8], by improving oxygenation [9, 10] and lung recruitment [11]. However, early COVID-19 pneumonia may be characterized by ventilation-perfusion inequalities [12], with little alveolar collapse and, hence, low recruitability [13, 14]. In this context, CPAP may induce overdistention [6], whereas a higher FiO₂ may provide adequate oxygenation and avoid potentially harmful effects of positive pressure.

Indeed, the few prospective investigations available in early COVID-19 pneumonia have suggested that CPAP does not reduce respiratory effort, nor the total lung stress [6, 15, 16]. However, CPAP was not compared with lower degrees of respiratory support (e.g., oxygen masks), and the isolated effects of FiO₂ titration were not evaluated.

Here, in patients with early COVID-19 pneumonia, we used Helmet-CPAP and oxygen masks to investigate the effects of positive pressure and FiO₂ on respiratory effort, lung stress, gas exchange and hemodynamics. We hypothesized that Helmet-CPAP would not reduce respiratory effort, and rather worsen lung stress and oxygenation when compared to oxygen masks with higher FiO₂.

Methods

Experimental setting

This study was conducted in the COVID-19 High-Dependency Unit (HDU) of the University Hospital San Luigi Gonzaga, Orbassano-Turin (Italy) from February 1st to June 30th, 2021. Ethical approval (San Luigi Gonzaga 1565/2021) and trial registration ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/NCT04885517): NCT04885517) were obtained. The experimental procedure is summarized in Fig. 1.

Inclusion and exclusion criteria

We included all confirmed SARS-CoV-2 patients with interstitial pneumonia (chest X-Ray or CT scan) who had been commenced on Helmet-CPAP by the treating clinicians within < 48 h (early pneumonia). We excluded patients with severe chronic pulmonary or cardiac

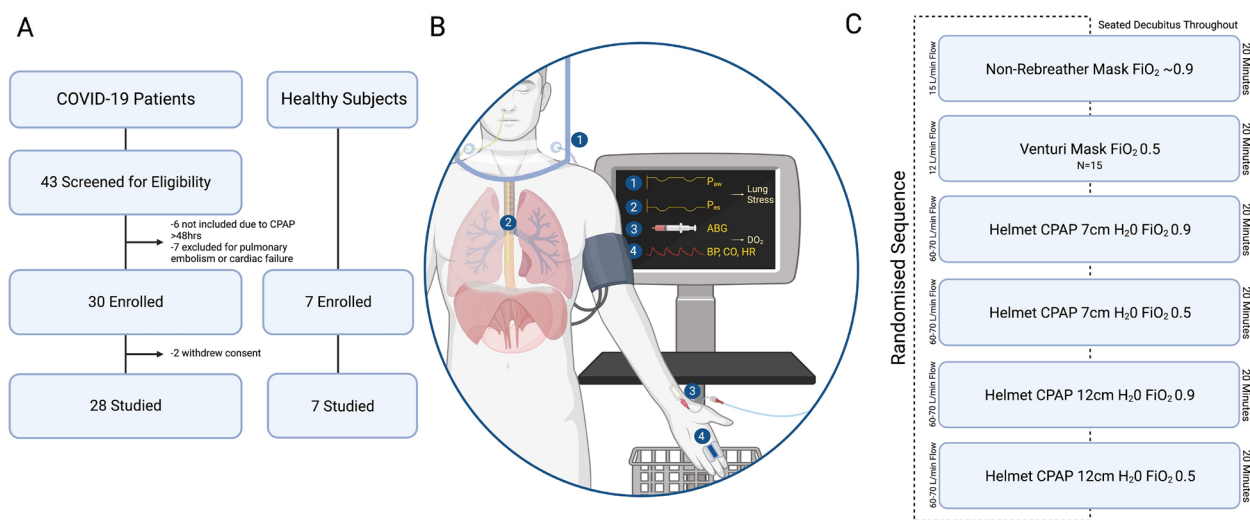


Fig. 1 Experimental procedure. **A:** Enrolment flowchart. Of note, 12 of the 28 COVID-19 patients were recruited prior to trial registration, but with ethics approval; **B:** experimental equipment and monitoring of (1) Helmet’s pressure (P_{aw}) and (2) esophageal pressure (P_{es}) through OptiVent™ monitor, (3) arterial blood gases (ABG) through radial line, (4) blood pressure (BP), cardiac output (CO) and heart rate (HR) through CNAP® monitor consisting of a finger cuff and a brachial cuff; Panel **C:** experimental protocol

disease, concomitant bacterial pneumonia, lobar or segmental pulmonary embolism at CT scan, or patients requiring immediate intubation (Additional file). Healthy volunteers were included as control group. All participants were non-sedated and provided written informed consent prior to enrolment.

Experimental equipment and monitoring systems

Participants were equipped with:

- A nasogastric catheter with an esophageal balloon (NutriVent™) advanced 35–40 cm from the nostrils and filled with 4 ml of air as per manufacturer instructions.
- A non-invasive device (CNAP® CNSystems-Medizintechnik-GmbH) for continuous arterial pressure and cardiac output measurement.
- A radial artery catheter for blood-gas analysis (patients only).

Experimental protocol

In the seated decubitus (trunk at 60°, legs down at 45°), participants underwent a random sequence of 20 min steps:

- (1) Non-rebreather mask (NRB), 15 L/min, FiO₂ ~0.9
- (2) Helmet-CPAP, 7 cmH₂O, FiO₂ 0.9, 60–70 L/min
- (3) Helmet-CPAP, 7 cmH₂O, FiO₂ 0.5, 60–70 L/min
- (4) Helmet-CPAP 12 cmH₂O, FiO₂ 0.9, 60–70 L/min
- (5) Helmet-CPAP 12 cmH₂O, FiO₂ 0.5, 60–70 L/min
- (6) Venturi mask (VM), 12 L/min, FiO₂ ~0.5 (performed in only a subset of patients)

The levels of Helmet-CPAP (7 and 12 cmH₂O) reflected our institution clinical guidance.

As all relevant variables except for the arterial oxygen tension (PaO₂) and saturation (SaO₂) were not significantly different between steps 2,3,4 and 5 (Additional file 1: Table S1), results related to these steps will be averaged and presented as a single step named “Helmet-CPAP”. PaO₂ and SaO₂ will be also presented relatively to single steps.

Measurements and calculations

The naso-gastric catheter (NutriVent™) and the Helmet (Dimar s.r.l.) were connected to a monitoring system (OptiVent™) continuously displaying esophageal and airway pressures. To ensure reproducibility, the esophageal balloon was deflated and reinflated before each measurement, and cardiac artifacts on the esophageal trace were sought to confirm its correct placement. At the end of each step, a stable breathing pattern for at least 2

minutes was sought before freezing the OptiVent™ monitor (Additional file 1: Figure S1). Esophageal and airway pressures were measured in five consecutive breaths and subsequently averaged. The work of breathing (WOB) scale [17], the Borg’s dyspnea scale [18], hemodynamics and blood gases were concomitantly evaluated.

Respiratory effort, the inspiratory Helmet’s pressure drop, and dynamic stress were computed, respectively, as the tidal swings in esophageal, airway, and their difference, i.e., the transpulmonary pressure [19]. The static stress associated with Helmet-CPAP was calculated as the change in end-expiratory transpulmonary pressure from NRB [20, 21]. Total stress was the sum of static and dynamic stress [6]. Oxygen delivery (DO₂) was calculated from cardiac index and the arterial oxygen content [22]. All equations are reported in the Additional file 1.

Study outcomes

The main outcome was the effect of positive pressure (NRB vs Helmet-CPAP) on respiratory effort and lung stress. Secondary outcomes were the effects of positive pressure on gas-exchange and hemodynamics, and the isolated effects of FiO₂ (NRB vs VM) on the same variables.

Sample size

Due to the physiological design of the study, and to the lack of comparable investigations at the time it was performed, a formal sample size was not calculated. Consistent with similar physiological studies [15, 16, 23, 24], we aimed to recruit a convenience sample size of 30 patients and 7 healthy controls.

Statistical analysis

Data are presented as mean ± standard deviation (SD). Normality was assessed with histograms and QQ plots, sphericity with Mauchly’s Tests. The effects of positive pressure (NRB vs Helmet-CPAP) and FiO₂ (NRB vs VM) were assessed with paired Student’s t-test or Wilcoxon signed rank test as appropriate. Multiple steps were compared with one-way repeated measures ANOVA or its nonparametric equivalent the Friedman test. Appropriate post-hoc tests were corrected for multiple comparisons using Holm’s p adjustment method. Pearson’s r coefficient of linear regressions was used to evaluate correlations between variables. Two-sided p values < 0.05 were considered statistically significant. R studio version 4.2.2 was used for statistical analysis.

Results

A flowchart describing patients’ enrolment is available in Fig. 1. As shown, among the 30 patients enrolled, 2 withdrew their consent because of discomfort, thereby

28 were eventually studied. Their characteristics are reported in Table 1. All 7 healthy controls were successfully studied. This group will be described separately.

Effects of positive pressure (NRB vs Helmet-CPAP)

Respiratory effort and lung stress

As shown in Table 2 and Fig. 2A, the esophageal swing increased in all but one patient from NRB to

Helmet-CPAP (5.0 ± 3.7 vs 8.3 ± 3.9 cmH₂O, $p < 0.01$), while clinical signs of effort (*i.e.*, respiratory rate, the WOB scale, and the Borg dyspnea scale) were not affected by positive pressure. The increase in esophageal swing (3.3 ± 1.5 cmH₂O) was paralleled by a comparable ($p = 0.16$) inspiratory drop in Helmet's pressure (-3.1 ± 1.0 cmH₂O, Additional file 1: Figure S1), thereby dynamic stress remained stable (Fig. 2B). Similarly, the static lung stress did not significantly change from NRB to Helmet-CPAP, but a high variability was observed: the change ranged from -4.5 to $+6.1$ cmH₂O, with a decrease in 10 patients (36%) and an increase in 18 patients (64%) (Fig. 2C). The total lung stress showed similar variability (range of change from -5.8 to $+5.7$ cmH₂O), remaining overall stable from NRB to Helmet-CPAP (Fig. 2D).

Table 1 Characteristics of COVID-19 patients (N = 28)

Anthropometric measures	
Age	65 ± 10
Female sex, N (%)	8 (29)
BMI, kg/m ²	28.8 ± 4.2
Comorbidities	
Smoke history, N (%)	14 (50)
Hypertension, N (%)	19 (68)
Diabetes mellitus, N (%)	6 (2)
COPD, N (%)	0 (0)
Congestive heart failure, N (%)	0 (0)
Chronic kidney disease, N (%)	0 (0)
COVID-19 history	
Days from symptoms onset	9 ± 3
Days from hospital admission	3 ± 5
Days from oxygen support	3 ± 3
Days from CPAP	1 ± 1
Previous awake proning, N (%)	11 (39)
Parameters at enrolment	
SOFA score	3 ± 1
CPAP (cmH ₂ O)	10 ± 1
FiO ₂	0.5 ± 0.1
SpO ₂	95 ± 5
Respiratory rate (bpm)	24 ± 5
WOB scale ^a	3 ± 1
Laboratory data	
White blood cells (10 ⁹ /L)	8.2 ± 3.2
Hemoglobin (g/dL)	13.9 ± 1.5
Platelet count (10 ³ /mL)	214 ± 80
D dimer (ng/mL)	919 ± 487
C-reactive protein (mg/L)	7.9 ± 5.1
Creatinine (mg/dL)	0.9 ± 0.2
Outcome	
ICU admission, N (%)	9 (32)
Endotracheal intubation, N (%)	8 (29)
In hospital death, N (%)	6 (21)

BMI body mass index, COPD chronic obstructive pulmonary disease, SOFA sequential organ failure assessment, CPAP continuous positive airway pressure, FiO₂ fraction of inspired oxygen, SpO₂ peripheral oxygen saturation, ICU intensive care unit

^a No patients showed nasal flaring, two had evident expiratory abdominal contraction, one demonstrated palpable inspiratory contraction of the sternocleidomastoid muscle

Determinants of respiratory effort and lung stress

During NRB, respiratory effort was higher in patients with lower PaO₂ (Additional file 1: Figure S2). The increase in respiratory effort from NRB to Helmet-CPAP correlated with the inspiratory Helmet's pressure drop (Additional file 1: Figure S3). Conversely, neither the PaO₂ nor the respiratory effort during NRB predicted changes in respiratory effort and lung stress due to the application of Helmet-CPAP (Additional file 1: Figure S4).

Gas exchange and hemodynamics

PaO₂ decreased from NRB (107 ± 55 mmHg) to Helmet-CPAP with FiO₂ 0.5 (86 ± 30 mmHg), while it increased with Helmet-CPAP with FiO₂ 0.9 (232 ± 92 mmHg). Positive pressure levels (7 vs 12 cmH₂O) did not affect the PaO₂ (Fig. 3A). Cardiac index significantly decreased from NRB to Helmet-CPAP (Table 2), thereby oxygen delivery remained unchanged even when PaO₂ increased (Fig. 3B).

Effects of FiO₂ (NRB vs VM)

The VM step was available in 15 patients. Compared to NRB, PaO₂ decreased, while respiratory effort, lung stress, and hemodynamics remained overall stable (Additional file 1: Table S2). However, when PaO₂ fell below 60 mmHg, we observed an increase in respiratory effort proportional to the degree of hypoxemia (Fig. 4A).

Healthy controls

The seven healthy controls had a mean age of 30 ± 2 years, 2 (29%) were female, BMI was 22.2 ± 2.9 kg/m². Table 2 and Fig. 2 report their response to Helmet-CPAP: the esophageal swing increased by 4.1 ± 1.3 cmH₂O, and an inspiratory Helmet's pressure drop was observed in all participants. The total lung stress increased by 3.1 ± 1.7

Table 2 Effects of positive pressure (NRB vs Helmet-CPAP)

Group	COVID-19 patients (N = 28)			Healthy controls (N = 7)		
	NRB	Helmet-CPAP	<i>p</i>	NRB	Helmet-CPAP	<i>p</i>
Respiratory support						
Respiratory effort, cmH ₂ O	5.0 ± 3.7	8.3 ± 3.9	<0.01	2.7 ± 0.8	6.7 ± 0.9	0.02
Helmet's pressure drop, cmH ₂ O	0 ± 0	-3.1 ± 1.0	<0.01	0 ± 0	-2.5 ± 0.6	<0.01
Dynamic stress, cmH ₂ O	5.0 ± 3.8	4.9 ± 3.8	0.97	2.7 ± 0.8	4.2 ± 0.5	0.03
Static stress, cmH ₂ O	0 ± 0	0.9 ± 2.4	0.07	0 ± 0	1.5 ± 2.0	0.08
Total stress, cmH ₂ O	5.0 ± 3.8	5.7 ± 5.0	0.09	2.7 ± 0.8	5.7 ± 2.0	0.02
Respiratory Rate, bpm	25 ± 5	25 ± 5	0.33	14 ± 2	14 ± 5	0.93
Work of breathing Scale (WOB)	2 ± 1	3 ± 1	0.37	1 ± 0	2 ± 0	<0.01
Borg dyspnea scale	0 ± 0	0 ± 0	0.16	0 ± 0	0 ± 0	>0.99
PaO ₂ , mmHg	107 ± 55	156 ± 57 ^a	<0.01	/	/	/
SaO ₂ , %	95 ± 6	96 ± 4	<0.01	/	/	/
PaCO ₂ , mmHg	36 ± 4	36 ± 3	0.23	/	/	/
pH	7.46 ± 0.02	7.46 ± 0.03	0.19	/	/	/
Systolic blood pressure, mmHg	136 ± 22	134 ± 19	0.54	116 ± 15	129 ± 11	0.06
Diastolic blood pressure, mmHg	77 ± 15	79 ± 12	0.50	70 ± 8	87 ± 10	0.02
Heart Rate, bpm	75 ± 14	74 ± 12	0.85	73 ± 9	75 ± 14	0.83
Cardiac index, L/min/m ²	3.2 ± 0.7	2.9 ± 0.5	0.02	3.4 ± 0.6	3.2 ± 0.5	0.09
Oxygen delivery, ml/min/m ^{2a}	577 ± 125	555 ± 115	0.18	/	/	/

^a See Fig. 3 for details about single Helmet-CPAP steps with different positive pressures and FiO₂. Measurement of airway pressure was missing in one patient

NRB non-rebreather mask, CPAP continuous positive airway pressure, PaO₂ partial pressure of arterial oxygen, SaO₂ percentage of oxygen saturated hemoglobin in arterial blood, PaCO₂ partial pressure of arterial carbon dioxide

cmH₂O, due to an increase in dynamic stress with an overall stable, but highly variable, static stress. The Helmet elicited expiratory abdominal contraction in 5 subjects, increasing the WOB scale. Cardiac output did not change with Helmet-CPAP.

Discussion

In this physiological study we investigated the effects of positive pressure and FiO₂, delivered with Helmet-CPAP and oxygen masks, on respiratory effort, lung stress, gas-exchange and hemodynamics in early COVID-19 pneumonia. We found that:

- (1) Helmet-CPAP increases respiratory effort without altering dynamic stress;
- (2) The effect of Helmet-CPAP on static and total stress is highly variable;
- (3) High FiO₂ has a greater impact than positive pressure on oxygenation;
- (4) FiO₂ affects respiratory effort only in the most hypoxic conditions.

Helmet-CPAP increases respiratory effort without altering dynamic stress

To the best of our knowledge, this is the first study reporting a systematic increase in respiratory effort associated with the application of Helmet-CPAP. Furthermore, by

measuring Helmet's pressure, we could demonstrate a dissociation between the increased respiratory effort and an unaltered dynamic stress. This finding is new, as the two variables are generally considered equivalent during CPAP [6, 8, 15].

While the inability of Helmet-CPAP to reduce dynamic stress was previously reported [6, 15, 16], and likely reflects low potential for lung recruitment in early COVID-19 pneumonia [13, 14], the increase in esophageal swing is less intuitive. A possible explanation is that the Helmet added an inspiratory load by not maintaining its pressure throughout the respiratory cycle [25, 26]. Indeed, to generate pressure in our Helmets, we used spring-loaded adjustable valves, which have been shown to cause airway pressure instability, similar to the one we observed in this study [27]. Interestingly, Menga et al. reported an increasing trend in respiratory effort with Helmet-CPAP compared to high flow nasal oxygen, but airway pressure was not monitored [15]. Conversely, no other study investigating the effects of Helmet-CPAP on respiratory effort had a baseline esophageal swing available for comparison, as patients kept breathing through the Helmet even when CPAP was set at zero cmH₂O [6, 16].

Although it would be tempting to solely ascribe the increase in esophageal swing to the concomitant inspiratory decrease in Helmet's pressure, the

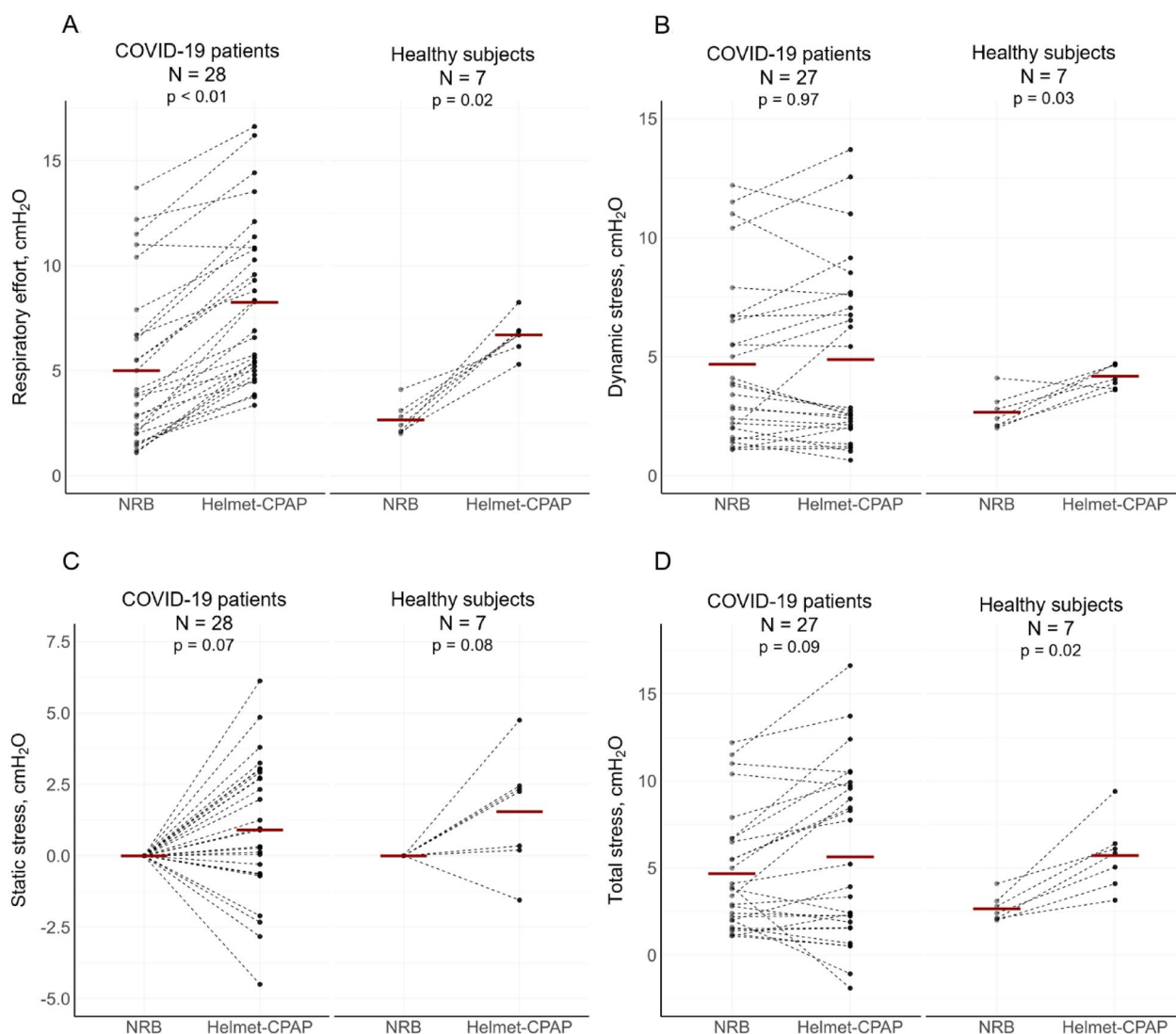


Fig. 2 Effects of positive pressure on respiratory effort and lung stress. Differences in respiratory effort (A), dynamic B, static C and total lung stress D between NRB and Helmet-CPAP in COVID-19 patients and Healthy subjects. Of note, measurement of airway pressure was missing in one patient. Black dots: single patients; Red bars: mean values; NRB Non-rebreather mask

correlation between the two variables was rather weak ($r=0.36$, Additional file 1: Figure S2). Another contributing factor may be expiratory muscle activation to limit increases in end expiratory lung volume (EELV) [28–31]. Indeed, relaxation of expiratory muscles at the onset of inspiration would increase the esophageal swing, mimicking inspiratory effort [32]. Although a gastric pressure trace would be required for confirmation, the lower than expected static stress associated with Helmet-CPAP in our patients might support this hypothesis (see below).

The effect of Helmet-CPAP on static and total stress is highly variable

Static stress represents the static transpulmonary pressure associated with CPAP. It has been previously estimated from passive properties of the respiratory system (normal lung to chest wall elastance ratio: $E_R=0.7$) [6, 33]. However, in spontaneously breathing patients with possible expiratory muscles activation [28–31, 34], direct assessment of changes in end-expiratory transpulmonary pressure ($P_{L(exp)}$), a proxy of changes in EELV [20, 21], might be a better option. Using this method, we

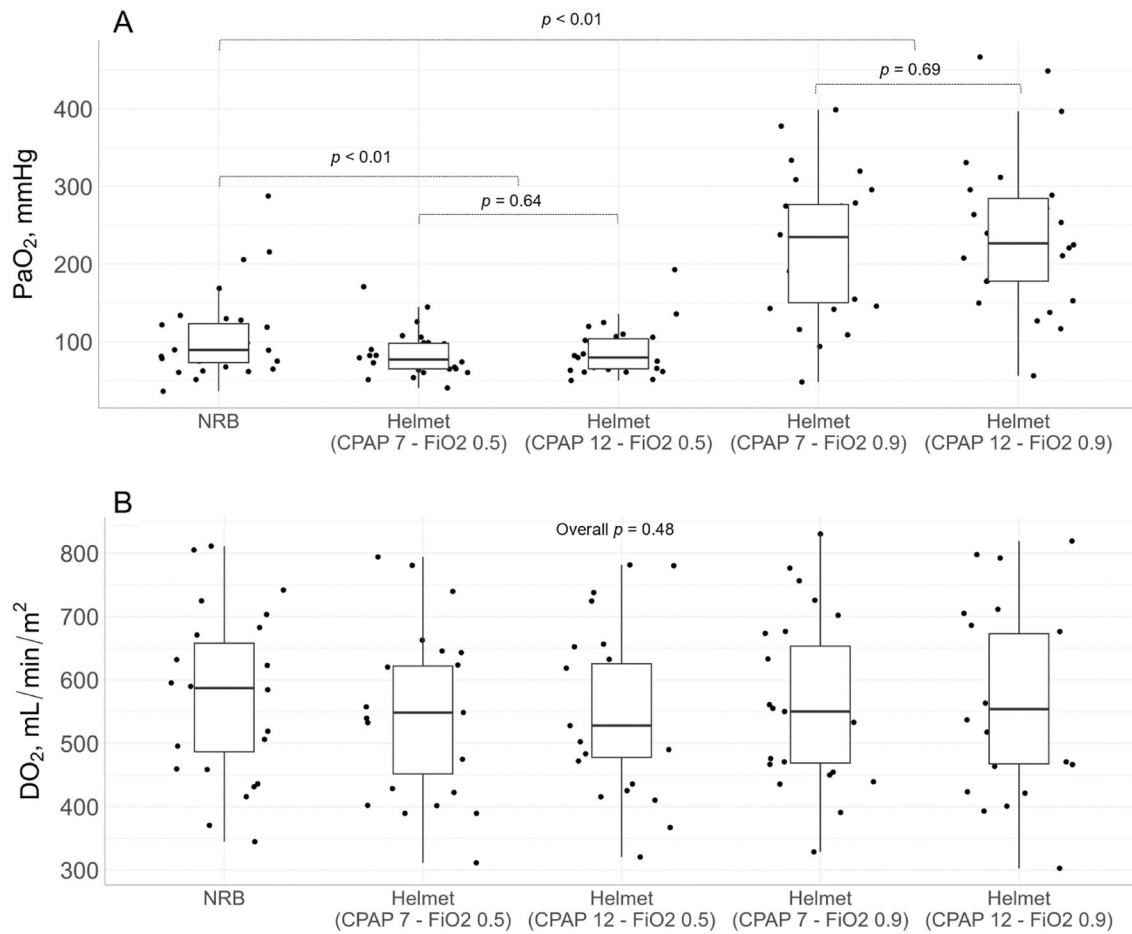


Fig. 3 Changes in PaO₂ and DO₂ with positive pressure and FiO₂. Changes in PaO₂ **A** and DO₂ **B** between steps in COVID-19 patients; The overall *p* value for the change in PaO₂ between the five steps was < 0.01 (not shown). Black dots: single patients; Boxplots: medians and interquartile ranges; PaO₂ arterial oxygen tension. NRB Non-rebreather mask. DO₂ oxygen delivery

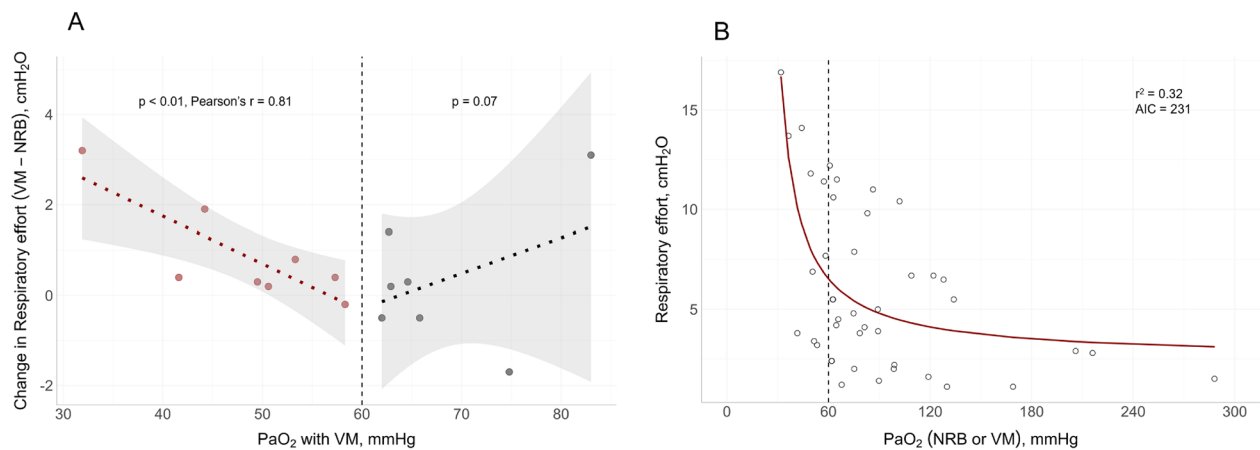


Fig. 4 Relationship between oxygenation and respiratory effort. **A**: relationship between PaO₂ during VM, and the change in respiratory effort from VM to NRB (*n* = 15): only in patients with PaO₂ < 60 mmHg (*n* = 8, red dots), a strong, significant relationship was found. **B**: relationship between PaO₂ and respiratory effort with oxygen masks (NRB and, when available, VM); PaO₂: arterial oxygen tension. NRB Non-rebreather mask, VM Venturi mask, AIC Akaike information criterion

found that Helmet-CPAP did not change static stress as would be predicted from the passive properties of the respiratory system (Additional file 1: Figure S5). Moreover, we observed a high variability between patients: some decreased or did not change static stress, suggesting expiratory muscle activation “protecting” their EELV [25, 28, 35]; others increased static stress, suggesting an increase in EELV. Such variability reflected on the total lung stress, which, overall, remained stable from NRB to Helmet-CPAP. This is at variance with previous studies estimating $P_{L(\text{exp})}$ from passive properties of the respiratory system and concluding that Helmet-CPAP inevitably increased the static, and thereby total lung stress [6]. Our findings suggest that the effects of Helmet-CPAP on $P_{L(\text{exp})}$ should be directly measured, as a high variability exists at a single patient level. Moreover, the response to Helmet-CPAP in terms of lung stress did not seem predictable from the baseline oxygenation or respiratory effort in our patients (Additional file 1: figure S4), further stressing the need for individualized assessment.

High FiO_2 has a greater impact than positive pressure on oxygenation

The preponderant role of FiO_2 over positive pressure in improving oxygenation in our patients is depicted in Fig. 3. Indeed, PaO_2 decreased from NRB to Helmet-CPAP with FiO_2 0.5, and was not affected by increasing CPAP levels. This is in line with ventilation-perfusion inequalities as major contributors to hypoxemia [12, 36], and with low potential for lung recruitment [13, 14] at this disease stage. Moreover, even with the higher PaO_2 reached during Helmet-CPAP with FiO_2 0.9, the concomitant decrease in cardiac output blunted any increase in oxygen delivery [22]. Taken together, these findings suggest that oxygen masks with high FiO_2 provide better oxygenation than Helmet-CPAP in early COVID-19 pneumonia.

FiO_2 affects respiratory effort only in the most hypoxic conditions

By altering FiO_2 in the absence of positive pressure (NRB vs VM), we observed an increase in respiratory effort only when PaO_2 fell below 60 mmHg (Fig. 4A). This supports that hypoxic drive plays a role only at very low oxygen tensions [9, 10, 37]. Indeed, the roughly hyperbolic relationship between respiratory effort and PaO_2 in our patients (Fig. 4B) resembles that obtained from carotid bodies in vitro [10] (details can be found in the Additional file). Interestingly, despite the very low PaO_2 reached during the VM step, no patient reported dyspnea, in line with the observed “silent hypoxemia” of early COVID-19 pneumonia [38].

Healthy subjects

The vast majority of our findings were confirmed in healthy subjects. Namely, the increase in esophageal swing, the inspiratory Helmet’s pressure drop, and the variable change in static stress with Helmet-CPAP. The visible contraction of abdominal muscles further suggests expiratory activation. The only notable difference in healthy controls was a significant increase in dynamic stress with Helmet-CPAP, suggesting that positive pressure might have increased their tidal volume, as previously reported [24, 39, 40].

Strengths and limitations

Strengths and novelties of this study are (1) the baseline step with oxygen masks, allowing detection of the inspiratory load added by the Helmet; (2) the contemporaneous measurement of esophageal and airway pressure, differentiating respiratory effort from dynamic stress during Helmet-CPAP; (3) the direct measurement of end-expiratory transpulmonary pressure to evaluate the static stress associated with Helmet-CPAP; (4) the simultaneous evaluation of blood gases and cardiac output to assess the effects of Helmet-CPAP on oxygen delivery; (5) the inclusion of a control group of healthy subjects. Limitations include the small sample size which, however, was similar to previous studies [15, 16, 23], in keeping with the complexity of these experiments. Other limitations are the lack of assessment of static lung volumes, tidal volume, inspiratory flow and gastric pressure, and the limited duration of the protocol steps (20 min): although this is similar to previous studies [6, 16], adaptation to CPAP (for example, reducing expiratory muscles activation) may require more time.

Conclusions

In early COVID-19 pneumonia, Helmet-CPAP increases respiratory effort, likely due to airway pressure instability during inspiration. A higher FiO_2 with oxygen masks provides better oxygenation with lower respiratory effort. The dynamic lung stress is not reduced by Helmet-CPAP, questioning its role in alleviating lung injury at this disease stage. The response of static and, thereby, total lung stress to Helmet-CPAP is highly variable, and cannot be predicted from the passive properties of the respiratory system. Multimodal monitoring of esophageal and airway pressure, blood gases and cardiac output allows thorough evaluation of the appropriateness of respiratory support at a single patient level.

Abbreviations

CPAP	Continuous positive airway pressure
FiO_2	Inspired oxygen fraction

NRB	Non-rebreather mask
VM	Venturi mask
COVID-19	Coronavirus infectious disease-19
ARF	Acute respiratory failure
EELV	End expiratory lung volume
E_R	Elastance ratio
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
SOFA	Sequential organ failure assessment
SpO ₂	Peripheral oxygen saturation
ICU	Intensive care unit
WOB	Work of breathing
PaO ₂	Partial pressure of arterial oxygen
SaO ₂	Percentage of hemoglobin saturated with arterial oxygen
PaCO ₂	Partial pressure of arterial carbon dioxide
CI	Cardiac index
DO ₂	Oxygen delivery

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13613-023-01202-0>.

Additional file 1: Figure S1. Esophageal and airway pressure measurement. **Figure S2.** Relationship between PaO₂ and respiratory effort with NRB. **Figure S3.** Relationship between the Helmet's inspiratory pressure drop and the increase in respiratory effort from NRB to Helmet-CPAP. **Figure S4.** Relationship between PaO₂ or respiratory effort with NRB and changes in respiratory effort or lung stress from NRB to Helmet-CPAP. **Figure S5.** Measured vs estimated static stress. **Table S1.** Invariance of variables during Helmet-CPAP steps. **Table S2.** Effects of FiO₂ (NRB vs VM).

Acknowledgements

Not Applicable.

Author contributions

LG, PC and AP designed the study; LG, MS, FC, SDB, MMM, LD, AL, FG, RP and MM performed the protocol; LG, IS, PDC and VR analyzed the data, prepared the tables and formulated the figures; LC and GB contributed to the interpretation of the findings; LG, PC, LC, PDC and GB drafted the manuscript which was then critically revised and approved by all authors. All authors read and approved the final version of the manuscript.

Funding

No part of the work presented has received financial support from any source.

Availability of data and materials

The dataset is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the local authority (San Luigi Gonzaga 1565/202). The study was performed according to local ethical standards and to the Helsinki Declaration of 1957. All participants signed a written informed consent prior to enrollment.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Department of Critical Care Medicine, Guy's and St. Thomas' National Health Service Foundation Trust, St. Thomas' Hospital, Westminster Bridge Road, London SE17EH, UK. ²Centre for Human and Applied Physiological Sciences, School of Basic and Medical Biosciences, King's College London, London, UK. ³Department of Pulmonary Medicine, AOU S. Luigi Gonzaga, Orbassano, Turin,

Italy. ⁴University of Turin, Turin, Italy. ⁵Department of Anesthesia and Critical Care, AOU S. Luigi Gonzaga, Orbassano, Turin, Italy. ⁶Department of Surgical Sciences, University of Turin, Turin, Italy. ⁷Department of Anaesthesia, Intensive Care and Emergency, Città della Salute e della Scienza University Hospital, Turin, Italy. ⁸Department of Oncology, University of Turin, Turin, Italy. ⁹Centre for Medical Sciences - CISMed, University of Trento, Trento, Italy. ¹⁰Department of Anesthesia and Intensive Care, Santa Chiara Regional Hospital, APSS Trento, Trento, Italy.

Received: 17 August 2023 Accepted: 6 October 2023

Published online: 17 October 2023

References

- Perkins GD, Ji C, Connolly BA, Couper K, Lall R, Baillie JK, et al. Effect of noninvasive respiratory strategies on intubation or mortality among patients with acute hypoxemic respiratory failure and COVID-19: the recovery-rs randomized clinical trial. *JAMA*. 2022;327:546–58.
- Grieco DL, Menga LS, Cesarano M, Rosà T, Spadaro S, Bitondo MM, et al. Effect of helmet noninvasive ventilation vs high-flow nasal oxygen on days free of respiratory support in patients with COVID-19 and moderate to severe hypoxemic respiratory failure: the HENIVOT randomized clinical trial. *JAMA*. 2021;325:1731–43.
- Sakuraya M, Okano H, Masuyama T, Kimata S, Hokari S. Efficacy of non-invasive and invasive respiratory management strategies in adult patients with acute hypoxaemic respiratory failure: a systematic review and network meta-analysis. *Crit Care*. 2021;25:414.
- Kumar V, Malik UA, Kumari R, Berkha KV, Kumar M, et al. Effectiveness of non-invasive respiratory support strategies in patients with COVID-19: a systematic review and meta analysis. *Ann Med Surg*. 2022;84:104827.
- Yoshida T, Torsani V, Gomes S, De Santis RR, Beraldo MA, Costa ELV, et al. Spontaneous effort causes occult pendelluft during mechanical ventilation. *Am J Respir Crit Care Med*. 2013;188:1420–7.
- Coppola S, Chiumello D, Busana M, Giola E, Palermo P, Pozzi T, et al. Role of total lung stress on the progression of early COVID-19 pneumonia. *Intensive Care Med*. 2021;47:1130–9.
- Cesarano M, Grieco DL, Michi T, Munshi L, Menga LS, Delle Cese L, et al. Helmet noninvasive support for acute hypoxemic respiratory failure: rationale, mechanism of action and bedside application. *Ann Intensive Care*. 2022;12:94.
- Grieco DL, Maggiore SM, Roca O, Spinelli E, Patel BK, Thille AW, et al. Non-invasive ventilatory support and high-flow nasal oxygen as first-line treatment of acute hypoxemic respiratory failure and ARDS. *Intensive Care Med*. 2021;47:851–66.
- Dripps RD, Comroe JH. The effect of the inhalation of high and low oxygen concentrations on respiration, pulse rate, ballistocardiogram and arterial oxygen saturation (oximeter) of normal individuals. *Am J Physiol*. 1947;149:277–91.
- López-Barneo J, González-Rodríguez P, Gao L, Fernández-Agüera MC, Pardal R, Ortega-Sáenz P. Oxygen sensing by the carotid body: mechanisms and role in adaptation to hypoxia. *Am J Physiol Cell Physiol*. 2016;310:C629–642.
- Morais CCA, Koyama Y, Yoshida T, Plens GM, Gomes S, Lima CAS, et al. High positive end-expiratory pressure renders spontaneous effort noninjurious. *Am J Respir Crit Care Med*. 2018;197:1285–96.
- Busana M, Giosa L, Cressoni M, Gasperetti A, Di Girolamo L, Martinelli A, et al. The impact of ventilation-perfusion inequality in COVID-19: a computational model. *J Appl Physiol*. 1985;2021(130):865–76.
- Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med*. 2020;46:1099–102.
- Pan C, Chen L, Lu C, Zhang W, Xia J-A, Sklar MC, et al. Lung recruitability in COVID-19-associated acute respiratory distress syndrome: a single-center observational study. *Am J Respir Crit Care Med*. 2020;201:1294–7.
- Menga LS, delle Cese L, Rosà T, Cesarano M, Scarascia R, Michi T, et al. Respective effects of helmet pressure support, continuous positive airway pressure and nasal high-flow in hypoxemic respiratory failure:

- a randomized crossover clinical trial. *Am J Respir Crit Care Med*. 2023;207:1310–23.
16. Lassola S, Miori S, Sanna A, Menegoni I, De Rosa S, Bellani G, et al. Assessment of inspiratory effort in spontaneously breathing COVID-19 ARDS patients undergoing helmet CPAP: a comparison between esophageal, transdiaphragmatic and central venous pressure swing. *Diagnostics*. 2023;13:1965.
 17. Apigo M, Schechtman J, Dhiliwayo N, Al Tameemi M, Gazmuri RJ. Development of a work of breathing scale and monitoring need of intubation in COVID-19 pneumonia. *Crit Care*. 2020;24:477.
 18. Borg GV. Psychophysical bases of perceived exertion. *Med Sci Sports Exercise*. 1982;14:377.
 19. Gattinoni L, Giosa L, Bonifazi M, Pasticci I, Busana M, Macri M, et al. Targeting transpulmonary pressure to prevent ventilator-induced lung injury. *Expert Rev Respir Med*. 2019;13:737–46.
 20. Schlobohm RM, Faltrick RT, Quan SF, Katz JA. Lung volumes, mechanics, and oxygenation during spontaneous positive-pressure ventilation: the advantage of CPAP over EPAP. *Anesthesiology*. 1981;55:416–22.
 21. Layon J, Banner MJ, Jaeger MJ, Peterson CV, Gallagher TJ, Modell JH. Continuous positive airway pressure and expiratory positive airway pressure increase functional residual capacity equivalently. *Chest*. 1986;89:517–21.
 22. Barthélémy R, Beaucoté V, Bordier R, Collet M, Gall AL, 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:e70–2.
 23. Tonelli R, Busani S, Tabbi L, Fantini R, Castaniere I, Biagioni E, et al. Inspiratory effort and lung mechanics in spontaneously breathing patients with acute respiratory failure due to covid-19: a matched control study. *Am J Respir Crit Care Med*. 2021;204:725–8.
 24. Patroniti N, Foti G, Manfio A, Coppo A, Bellani G, Pesenti A. Head helmet versus face mask for non-invasive continuous positive airway pressure: a physiological study. *Intensive Care Med*. 2003;29:1680–7.
 25. Katz J, Kraemer R, Gjerde G. Inspiratory work and airway pressure with continuous positive airway pressure delivery systems. *Chest*. 1985;88:519–26.
 26. L'Her E, Deye N, Lellouche F, Taille S, Demoule A, Fraticelli A, et al. Physiologic effects of noninvasive ventilation during acute lung injury. *Am J Respir Crit Care Med*. 2005;172:1112–8.
 27. Isgrò S, Zanella A, Giani M, El Aziz Abd, El Sayed DS, Pesenti A, Patroniti N. Performance of different PEEP valves and helmet outlets at increasing gas flow rates: a bench top study. *Minerva Anestesiol*. 2012;78:1095–100.
 28. Shi Z-H, Jonkman A, de Vries H, Jansen D, Ottenheijm C, Girbes A, et al. Expiratory muscle dysfunction in critically ill patients: towards improved understanding. *Intensive Care Med*. 2019;45:1061–71.
 29. Gothe B, Cherniack NS. Effects of expiratory loading on respiration in humans. *J Appl Physiol*. 1980;49:601–8.
 30. Martin JG, De Troyer A. The behaviour of the abdominal muscles during inspiratory mechanical loading. *Respir Physiol*. 1982;50:63–73.
 31. Jansen D, Jonkman AH, de Vries HJ, Wennen M, Elshof J, Hoofs MA, et al. Positive end-expiratory pressure affects geometry and function of the human diaphragm. *J Appl Physiol*. 1985;2021(131):1328–39.
 32. Lessard MR, Lofaso F, Brochard L. Expiratory muscle activity increases intrinsic positive end-expiratory pressure independently of dynamic hyperinflation in mechanically ventilated patients. *Am J Respir Crit Care Med*. 1995;151:562–9.
 33. Weaver L, Das A, Saffaran S, Yehya N, Chikhani M, Scott TE, et al. Optimising respiratory support for early COVID-19 pneumonia: a computational modelling study. *Br J Anaesth*. 2022;128:1052–8.
 34. Chandra A, Coggeshall JW, Ravenscraft SA, Marini JJ. Hyperpnea limits the volume recruited by positive end-expiratory pressure. *Am J Respir Crit Care Med*. 1994;150:911–7.
 35. Gherini S, Peters RM, Virgilio RW. Mechanical work on the lungs and work of breathing with positive end-expiratory pressure and continuous positive airway pressure. *Chest*. 1979;76:251–6.
 36. Giosa L, Payen D, Busana M, Mattei A, Brazzi L, Caironi P. Orthodeoxia and its implications on awake-proning in COVID-19 pneumonia. *Crit Care*. 2021;25:429.
 37. Vaporidi K, Akoumianaki E, Telias I, Goligher EC, Brochard L, Georgopoulos D. Respiratory drive in critically ill patients. pathophysiology and clinical implications. *Am J Respir Crit Care Med*. 2020;201:20–32.
 38. Busana M, Gasperetti A, Giosa L, Forleo GB, Schiavone M, Mitacchione G, et al. Prevalence and outcome of silent hypoxemia in COVID-19. *Minerva Anestesiol*. 2021;87:325–33.
 39. Urbscheit N, Bishop B, Bachofen H. Immediate effects of continuous positive pressure breathing on abdominal expiratory activity, minute ventilation, and end-tidal P CO₂ of conscious man. *Phys Ther*. 1973;53:258–66.
 40. Xiao S, Lu Y, Guo H-X, Qiu Z, Luo Y. Effect of expiratory load on neural inspiratory drive. *Chin Med J (Engl)*. 2012;125:3629–34.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Submit your manuscript to a SpringerOpen[®] journal and benefit from:

- Convenient online submission
- Rigorous peer review
- Open access: articles freely available online
- High visibility within the field
- Retaining the copyright to your article

Submit your next manuscript at ► [springeropen.com](https://www.springeropen.com)