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Research article

The "ZEEP-PEEP test" to evaluate the response to positive end-expiratory pressure delivered by helmet: A prospective physiologic study

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ABSTRACT

Introduction: The improvement in oxygenation after helmet application in hypoxemic patients may be explained by the alveolar recruitment obtained with positive end expiratory pressure (PEEP) or by the administration of a more accurate inspiratory fraction of oxygen (F_iO_2). We have designed the "ZEEP-PEEP test", capable to distinguish between the F_iO_2-related or PEEP-related oxygenation improvement. Our primary aim was to describe the use of this test during helmet CPAP to assess the oxygenation improvement attributable to PEEP application.

Material and methods: We performed a prospective physiological study including adult critically ill patients. Respiratory and hemodynamic parameters were recorded before helmet application (PRE step), after helmet application without PEEP (ZEEP step) and after the application of the PEEP valve (PEEP step), while maintaining a constant FiO_2. We defined as "PEEP responders" patients showing a PaO_2/FiO_2 ratio improvement $\geq$10% after PEEP application.

Results: 93 patients were enrolled. Compared to the PRE step, PaO2/FiO2 ratio was significantly improved during helmet CPAP both at ZEEP and PEEP step (189 $\pm$ 55, 219 $\pm$ 74 and 241 $\pm$ 82 mmHg, respectively, $p < 0.01$). Both PEEP responders (41%) and non-responders showed a significant improvement of PaO2/FiO2 ratio after the application of helmet at ZEEP, PEEP responders also showed a significant improvement of oxygenation after PEEP application (208 $\pm$ 70 vs 267 $\pm$ 85, $p < 0.01$).

Conclusions: Helmet CPAP improved oxygenation. This improvement was not only due to the PEEP effect, but also to the increase of the effective inspired FiO_2. Performing the ZEEP-PEEP test may help to identify patients who benefit from PEEP.

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1. Introduction

Non-invasive respiratory support can serve as an initial treatment for patients with acute hypoxemic respiratory failure, potentially reducing the rate of endotracheal intubation and its related complications such as ventilator-associated pneumonia, delirium and ICU-acquired weakness [1,2]. Non-invasive continuous positive airway pressure (CPAP) has proven effective to improve gas exchange and to prevent endotracheal intubation in respiratory failure from different etiologies [3,4]. CPAP improves respiratory mechanics and gas exchanges by maintaining a constant positive end expiratory pressure (PEEP) and delivering inspiratory oxygen fractions up to 100%. Non-invasive CPAP can be delivered by nasal/full-face masks or by helmet [5]. The helmet is a transparent plastic hood which holds the entire head of the patient, while a latex-free collar on the lower side of the hood provides a soft seal around the patient's neck to avoid air leaks [3,6]. In the last few years, the use of the helmet as an interface for non-invasive respiratory support has steadily increased, since it is usually well tolerated [6] and allows longer and continuative CPAP treatment compared with other interfaces [7].

From a clinical point of view, the improvement of oxygenation following helmet application is commonly used to identify patients who may benefit from CPAP. However, the improvement of oxygenation observed after helmet CPAP application may be attributed either to the PEEP effect or to the effective delivery of the intended inspiratory oxygen fraction (F_iO_2). In fact, when oxygen is delivered with other techniques (e.g. standard O_2 masks of high flow nasal cannulae – HFNC), room air may enter the patient's airways, thus reducing the actual inspiratory oxygen fraction [8,9]. The difference between the intended and actual oxygen fraction might be further increased in patients with severe respiratory failure, who may show inspiratory flows as high as 1–2 L/s[8]. Contrarily, helmet acts as a closed system, providing a constant and exact F_iO_2, whatever the respiratory pattern.

To investigate the effective response to PEEP after helmet application, we designed a test called "ZEEP-PEEP test" that consists in evaluating the changes in oxygenation between helmet without PEEP (zero end expiratory pressure – ZEEP) as compared to helmet with PEEP, while maintaining the same F_iO_2.

The aim of the present study was to prospectively evaluate the ZEEP-PEEP test in a cohort of critically ill patients with a clinical indication for helmet CPAP. Specifically, our objective was to evaluate the extent to which the improvement in oxygenation can be attributed to the application of PEEP.

2. Materials and methods

2.1. Study design and population

The study was approved by the local Ethics Committee in May 2022 (Comitato Etico Brianza - ref. n. 509–2022).

We conducted a prospective physiological single-center study including adult patients admitted to the ICU of Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy, from June 1, 2022 to June 31, 2023. We enrolled consecutive patients with respiratory failure with clinical indication for CPAP therapy. Patients who did not express a written informed consent were excluded from the study. We also excluded patients receiving oxygen by a non-rebreather mask, due to the unpredictability of the delivered F_iO_2[9]

2.2. Protocol

The study included three steps.

1 – PRE parameters were gathered with the oxygen delivery method in use (i.e. high flow nasal cannulas –HFNC– or Venturi Mask -VM-).
2 – ZEEP helmet was applied without the PEEP valve
3 – PEEP the PEEP valve was applied, and the PEEP level was set according to clinical indications.

For each timepoint, we recorded parameters regarding arterial blood gas analysis, hemodynamics (heart rate and blood pressure) and respiration (respiratory rate and peripheral O_2 saturation). Data collection and arterial blood gas sampling were performed before helmet application (PRE step), then 10 min after helmet application without PEEP (ZEEP step) and 1 h after the PEEP was applied (PEEP step). F_iO_2 was maintained along the three steps.

During HFNC and helmet treatment, the gas flow was delivered by a venturi flow generator (DIMAR S.r.l., Medolla, Italy). The delivered O2 fraction was checked via an oxygen analyzer (Handi+, Maxtec, Salt Lake City, UT). The fresh gas flow during helmet treatment test was set above 60 L/min to minimize CO2 rebreathing. The DimAir 500/9666 helmet (DIMAR S.r.l., Medolla, Italy) was used in all patients. The pressure inside the helmet was measured by the mechanical manometer combined with the device [10]. During the ZEEP step, the pressure inside the hood was constantly negligible, as previously reported when no PEEP valve is applied to the helmet outlet [10,11].

2.3. Statistical analysis

Continuous variables were reported as mean ± standard deviation or as median and 25th-75th percentile, as appropriate, categorical data as absolute (relative) frequency. Comparisons among the three steps in the general population and after stratification in PEEP responders and non-responders were assessed by means of Wilcoxon Signed Rank test, the Bonferroni correction was applied for multiple comparison.

Patients were stratified into subgroups based on the method of O_2 delivery at baseline (HFNC vs venturi mask) and based on their response to PEEP. We defined a patient "PEEP responder" when we observed a PaO_2/FiO_2 ratio improvement of more than 10% after PEEP application [12]. The response to PEEP was explored in predefined clinically relevant subgroups, and its probability (calculated by univariate logistic regression) was expressed by odd ratios with their confidence interval.

A two-tailed level of significance of 0.05 was assumed.

2.4. Sample size

Based on preliminary data, the prevalence of PEEP responders was estimated at 50%. We defined ±10% as an acceptable margin of error for this percentage. Considering a confidence interval of 95%, a sample size of 88 patients was calculated (svysampsi command, Stata/MP 17.0, StataCorp LLC, College Statio, TX). Assuming a proportion of missing data of 5%, a sample size of at 93 patients was estimated.

3. Results

99 consecutive patients underwent helmet CPAP for respiratory failure in the study period. 6 patients receiving oxygen by a non-rebreather mask before helmet CPAP were excluded. 93 patients were then enrolled in the study. All patients expressed their informed consent. CPAP was used mainly in the post extubation setting (75 patients, 81%), whereas it was used in the acute non-intubated patient in the remaining 19% of cases. 25 (27%) patients were females, median age was 63 (53–71) years, BMI was 26 (24–29). The most common causes of respiratory failure in this cohort were pneumonia (47, 50%), of which 39% were COVID-19 related, and trauma (16,17%). The main comorbidities and the diagnosis at the ICU admission of the study population are summarized in Table S1 (Supplementary Material).

Before the application of helmet CPAP, oxygen was mainly delivered with Venturi Mask (54, 58%), whereas the remaining 39 patients (42%) were treated with HFNC.

Median F_iO_2 was 50 (40–50) %, PEEP during the PEEP step was set at 8 (8-8) cmH_2O, ranging from 5 to 10. Helmet CPAP significantly improved oxygenation: PaO_2/FiO_2 ratio was significantly improved both at ZEEP and PEEP step, compared to PRE step (Fig. 1). Concurrently, SpO_2 and SaO_2 were significantly improved at ZEEP and PEEP step compared to step PRE (Table 1).

38 (41%) of the patients in our cohort were PEEP responders, whereas the remaining 55 patients did not increase their PaO_2/FiO_2 ratio after PEEP application. Fig. 2 shows the different patterns of PaO_2/FiO_2 ratio variation along the three steps within each subgroup. Both subpopulations showed a significant increase in oxygenation parameters when helmet was applied without PEEP (step 2-ZEEP). Only in PEEP responders, a significant improvement of PaO_2/FiO_2 ratio was recorded after application of PEEP.

Figure S1 (Supplementary material) present the changes in PaO_2/FiO_2 ratio after stratification of the study population based on the O_2 delivery method at baseline. The improvement of PaO_2/FiO_2 ratio from step PRE to step ZEEP was significantly greater in patients on Venturi mask: +34 mmHg (8–64) mmHg compared to +19 (−5 - 42) in the HFNC subgroup, respectively, $p = 0.046$. The improvement of PaO_2/FiO_2 ratio from step ZEEP to step PEEP did not differ between the two subgroups: +14 (−1 – 58) vs +14 (3–31) mmHg in patients who were on HFNC and Venturi mask at baseline, respectively. Fig. S2 (Supplementary material) depict the oxygenation response along the three steps, stratified into PEEP responders and non-responders in patients treated at baseline with

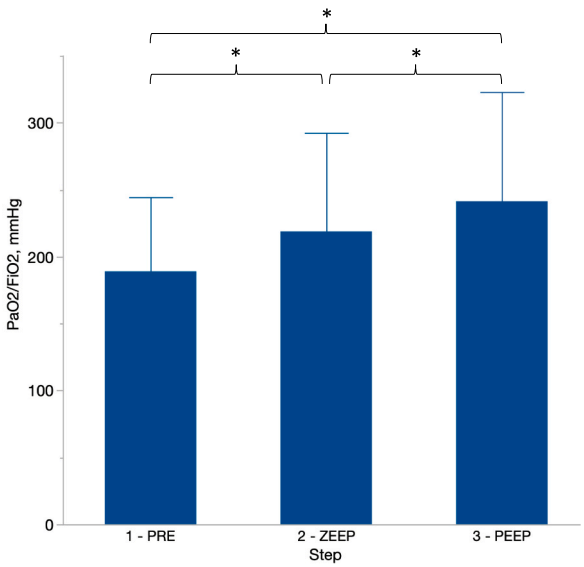

Fig. 1. Changes in arterial oxygen tension to inspired oxygen fraction ratio (PaO_2/FiO_2, mmHg) along the three steps. Data are presented as means and standard deviation. * = $p < 0.05$.

Table 1
shows the respiratory and hemodynamic parameters along the three steps of the study.

	1 - PRE	2 - ZEEP	3 - PEEP
PaO_2, mmHg	85 ± 20	98 ± 26[a]	109 ± 35[a,b]
PaO_2/FiO_2, mmHg	189 ± 55	219 ± 74[a]	241 ± 82[a,b]
pH	7.46 ± 0.04	7.456 ± 0.039	7.455 ± 0.04
$PaCO_2$, mmHg	41 ± 7	41 ± 7	41 ± 7
Haemoglobin, g/dL	10.5 ± 1.6	10.4 ± 1.7	10.4 ± 1.7
SaO_2, %	95.1 ± 2.5	96.1 ± 2.1[a]	96.7 ± 1.8[a,b]
SpO_2, %	96 ± 3	97 ± 2[a]	97 ± 2[a,b]
Respiratory rate, breaths/minute	20 ± 6	20 ± 5	20 ± 5
Systolic arterial pressure, mmHg	138 ± 21	140 ± 24	138 ± 22
Diastolic arterial pressure, mmHg	68 ± 13	70 ± 13	71 ± 15
Heart rate, beats/minute	89 ± 17	89 ± 16	88 ± 16
Lactate, mmol/L	1.42 ± 2.06	1.36 ± 2.1	1.35 ± 2.13

Blood gas results, respiratory parameters and hemodynamics along the study. PaO_2, arterial oxygen tension; PaO_2/FiO_2, arterial oxygen tension to inspired oxygen fraction ratio in mmHg; $PaCO_2$, arterial carbon dioxide tension; HbO_2, arterial haemoglobin saturation; SpO_2, peripheral oxygen saturation.

[a] $p < 0.05$ vs step 1 – PRE.

[b] $p < 0.05$ vs step 2 – ZEEP.

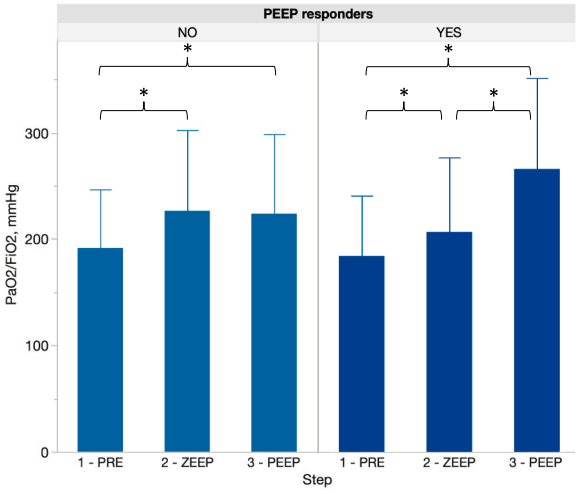

Fig. 2. Oxygenation response stratified by population subgroups: PEEP non-responders (left panel, light blue) and PEEP responders (right panel, dark blue). Data are presented as means and standard deviation. * = $p < 0.05$. PaO_2/FiO_2, ratio of arterial oxygen tension to inspiratory oxygen fraction. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

HFNC (Fig. S2A) or Venturi (Fig. S2B).

The PEEP response in predefined clinically relevant subgroups is analysed in Fig. 3. No significant association between subgroups and PEEP response was recorded. A trend towards a positive response was recorded in the most hypoxic patients (OR 2.34).

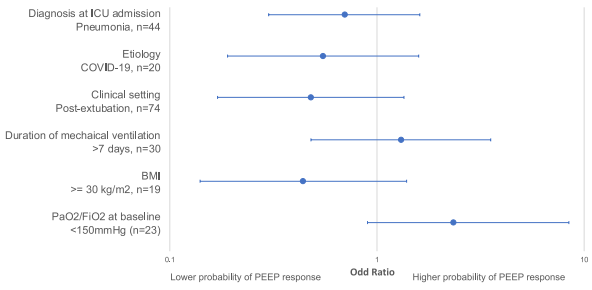

Fig. 3. Probability of oxygenation response to positive end expiratory pressure (PEEP) in clinically relevant subgroups. ICU, intensive care unit; BMI, body mass index; PaO_2/FiO_2, ratio of arterial oxygen tension to inspiratory oxygen fraction.

4. Discussion

In this population mainly characterized by patients with pneumonia-related acute respiratory failure in the post extubation setting, helmet application resulted in an improvement in gas exchange compared to oxygen therapy delivered with high flow nasal cannulas or Venturi mask. The ZEEP-PEEP test allowed to discriminate patients who benefit from PEEP application (i.e. PEEP responders) from patients where the increase of the PaO_2/FiO_2 ratio is only secondary to the correct delivery of the intended (i.e. higher) F_iO_2. In our population, the proportion of patients with a clinical response to PEEP was 41%.

Continuous Positive Airway Pressure (CPAP) is a non-invasive respiratory support modality which allows to deliver a constant PEEP level throughout the respiratory cycle. The application of PEEP in patients with acute respiratory failure may enhance alveolar recruitment and decrease atelectasis, thus reducing the pulmonary shunt fraction [13–16]. Moreover, PEEP may reduce the interstitial oedema, ameliorating the O_2 diffusion capacity of the alveolocapillary barrier [17], thus reducing the alveolo-arterial gradient and improving arterial O_2 tension. The non-invasive application of PEEP may thus prevent the need for more invasive interventions like endotracheal intubation and mechanical ventilation [2,18–20].

In addition to the above-mentioned effect on gas exchanges of PEEP, the improvement in gas exchange observed with helmet CPAP may be due to the accurate delivery of the intended inspiratory oxygen fraction set by the physician, making it more reliable compared to other oxygen therapy devices. Actually, the helmet acts as a semi-closed environment [6], working as an advanced "oxygen tent", allowing to deliver fractions of oxygen as high as 100% [21]. The patient inspiratory fraction during helmet treatment is then identical to the set oxygen concentration [22,23]. For this reason, the F_iO_2 delivered with the helmet turns out to be higher than that delivered breathing with devices that work at lower flows with an "open" interface (i.e. venturi masks and HFNC), even if the set O_2 fraction is the same. The use of the ZEEP-PEEP test seems of robust clinical relevance in patients treated with both Venturi mask and HFNC at baseline, in which the actual F_iO_2 might be markedly overestimated and, consequently, the PaO_2/FiO_2 ratio underestimated. Of note, in patients who received HFNC, the change in PaO_2/FiO_2 ratio from PRE to ZEEP was smaller. Nonetheless, it should be noted that, when transitioning from HFNC to helmet-ZEEP, the low PEEP-effect characteristic of HFNC is lost and this could mitigate the relative rise in the PaO_2/FiO_2 ratio observed.

It is then of great importance identifying patients who benefit from PEEP, as applying positive airway pressure is a therapy which is not devoid of potential adverse effects, such as hemodynamic impairment and barotrauma. The identification of non-responders may avoid the use of PEEP in patients for whom it may be dangerous (e.g., hypovolemia or haemorrhagic shock) and to avoid CPAP treatment in conditions when it may be undesirable (e.g. head and neck trauma or burns) or poorly tolerated. In the present work, we presented the use of a novel clinical test to evaluate the response to PEEP. The ZEEP-PEEP test allowed to distinguish a subgroup of patients who responded to PEEP from patients whose oxygenation improved only due to the higher F_iO_2 delivered with the helmet, with no additional benefit from positive pressure. The analysis of predefined clinically relevant subgroups did not identify any category of patients with a significantly higher probability of benefit from PEEP. We observed a trend indicating an increased likelihood of positive end-expiratory pressure (PEEP) effectiveness in the most hypoxic patients at baseline. On the other hand, Conversely, the analysis unexpectedly revealed a trend toward a diminished response to PEEP in obese patients. It can be speculated that non-obese patients with an indication for CPAP may have presented a more severe lung condition [24]. However, no predictors of an effective response to PEEP have been identified, highlighting the need of evaluating the patient response to PEEP by the proposed test. We believe that the ZEEP-PEEP test may help the clinician to identify the respiratory support that best fits the patient's pathophysiological needs.

Our work presents some limitations. First, we studied a population of patients who mainly required respiratory support in the post-extubation setting. In this scenario, non-invasive respiratory support is commonly used to support oxygenation and spontaneous ventilation with a pre-emptive and not therapeutic purpose, in order to "protect" extubation [23,25]. Moreover, the patient with a certain degree of oxygenation impairment right after discontinuation of mechanical ventilation is likely less severe than a patient in the acute phase of respiratory failure. For these reasons, although pathophysiological features of impairment of gas exchange after extubation and in the acute phase are substantially the same [26], our results may not be generalized. Second, we assessed the benefit of PEEP exclusively through the PaO2/FiO2 ratio, employing a 10% cut-off which was selected arbitrarily. However, compared to other parameters (i.e. pulmonary shunt fraction) changes in PaO_2/FiO_2 may also be influenced by hemodynamic and thus may not reflect lung recruitment, due to the potential hemodynamic impairment of PEEP. We did not perform any invasive hemodynamic measurement or blood sampling for central venous saturation, which may have provided insights on the hemodynamic impact of PEEP in our population. However, systemic arterial pressure and heart rate did not show any modification, therefore relevant hemodynamic effect were unlikely. Third, the response to PEEP was evaluated 60 min after its application. However, a subset of patients may exhibit a delayed response to PEEP. Additionally, the relatively low level of PEEP might have been insufficient, especially for those with a more severe disease. Consequently, we may have underestimated the percentage of patients who may benefit from CPAP treatment.

5. Conclusion

In a population mainly characterized by patients with pneumonia-related respiratory failure in the post-extubation setting, helmet application significantly improved oxygenation. This improvement is not only due to PEEP, but also to the increase of the actual F_iO_2 delivered. Less than a half of the patients were PEEP responders. Performing the ZEEP-PEEP test allowed to assess the impact of PEEP on the improvement of oxygenation during helmet CPAP and may select patients who benefit from PEEP application.

CRediT authorship contribution statement

Marco Giani: Writing – review & editing, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Benedetta Fumagalli:** Writing – original draft. **Francesco Cipulli:** Writing – review & editing. **Emanuele Rezoagli:** Writing – review & editing, Methodology. **Matteo Pozzi:** Writing – review & editing, Methodology. **Denise Fumagalli:** Writing – review & editing. **Letizia Fumagalli:** Writing – review & editing. **Katia Ferrari:** Writing – review & editing. **Roberto Rona:** Writing – review & editing. **Giacomo Bellani:** Writing – review & editing, Methodology. **Alberto Lucchini:** Writing – review & editing, Conceptualization. **Giuseppe Foti:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28339.

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