Helmet CPAP to Treat Hypoxic Pneumonia Outside the ICU: An Observational Study During the COVID-19 Outbreak

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Research

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Abstract

Background: Respiratory failure due to COVID-19 pneumonia is associated with high mortality and may threaten healthcare systems hold, due to the surge patients requiring advanced respiratory support. Shortage of intensive care unit (ICU) beds required many patients to be treated outside the ICU despite severe hypoxia. Helmet is as effective interface to provide Continuous Positive Airway Pressure (CPAP) non-invasively. We report data about the usefulness of helmet CPAP during pandemic, either as an effective treatment, a bridge to intubation or a rescue therapy for patients with care limitations (DNI).

Methods: In this observational study we collected data regarding patients failing standard oxygen therapy (i.e. non-rebreathing mask) due to COVID-19 pneumonia treated with a free flow helmet CPAP system. Patients' data were recorded before, at initiation of CPAP treatment and once a day, since. CPAP failure was defined as a composite outcome of intubation or death.

Results: A total of 306 patients were included; 42% were deemed as DNI. Helmet CPAP treatment was successful in 69% of the full-treatment and 29% of the DNI patients (P<0.001). With helmet CPAP, PaO_2/FiO_2 ratio doubled from about 100 to 200 mmHg (P<0.001); respiratory rate decreased from 28 [22-32] to 24 [20-29] breaths per minute, P<0.001). CPAP failure was independently associated with CRP, time to oxygen mask failure, age, PaO_2/FiO_2 during CPAP, number of comorbidities. Helmet CPAP was maintained for 6 [3-9] days, almost continuously during the first two days. None of the full treatment patients died before intubation in the wards

Conclusions: Helmet CPAP treatment is feasible for several days outside the ICU, despite persisting hypoxia. It is effective, avoiding intubation in the majority of full treatment patients when standard oxygen therapy fails. DNI patients could benefit from helmet CPAP as rescue therapy to improve survival.

Trial Registration: NCT04424992

Background

In the early months of 2020 a massive COVID-19 pneumonia outbreak hit Italy. During the pandemic illness, an overwhelming number of patients suffering from hypoxaemic respiratory failure presented to hospitals' emergency rooms, burdening the health system to an unexpected extent. To face such a number of critical patients, intensive care beds were more than doubled, with an occupancy close to 100%.[1]

One of the effective treatments for respiratory failure, particularly if applied early and in less severe patients, is non-invasive ventilation.[2, 3] As an example, Continuous Positive Airway Pressure (CPAP) delivered non-invasively by helmet proved superior to non-rebreathing oxygen mask in community-acquired pneumonia.[4, 5] The optimal treatment of COVID-19 pneumonia is still under debate, and some experts believe that providing a moderate level (<10 cmH_2O) of Positive End-Expiratory Pressure (PEEP)

can match patient's need during the first phase of the disease, albeit this must be balanced with the potential risk of delayed intubation.[6-8]

The rationale for using helmet CPAP is that it is effective for treatment of respiratory failure, and presents many advantages as compared to non-invasive ventilation mask interface.[9, 10] In fact, it is generally well tolerated, air leaks are rarely an issue and it is associated with low pressure ulcer complications, particularly for prolonged therapy.[11] When treating COVID-19 affected patients, the use of helmets might bear the additional advantage of reducing virus environment contamination.[12, 13] Recent reports suggest that helmet CPAP can be effective for COVID-19 treatment,[14-16] possibly combined with prone or lateral position.[17-19] In a multicenter cohort study Aliberti et al. showed that helmet CPAP significantly increased PaO2/FiO2 from oxygen administration alone, but that treatment failure was frequent, occurring in 44% of patients who required intubation and invasive ventilation.[20]

Early recognition of patients at high risk of treatment failure is crucial, both for individual treatment and resources allocation. We present the outcomes associated with treatment of respiratory failure with helmet CPAP during the COVID-19 outbreak in our hospital consortium, an approach which has been widely applied in Northern Italy. The primary aim of the present study is to describe the effects of helmet CPAP treatment during the COVID-19 pandemic, identifying early predictors of CPAP failure. Secondary endpoints were the description patients' outcomes based on the presence of ceiling of care.

Methods

This is a retrospective observational cohort study regarding patients treated with helmet CPAP from March 3 to April 3, 2020. Data were collected in a local online registry as part of the STORM study (Spallanzani Institute approval number 84/2020; NCT04424992). Patients' consent was waived.

Organizational aspects

The study was conducted in the two hospitals of the ASST Monza (San Gerardo Hospital and Desio Hospital), which include a total of approximately 1200 beds, with about 35 ICU beds, before COVID-19 increased up to one-hundred during the rurge. Several medical and surgical wards were converted in COVID-19 wards, capable of applying non-invasive CPAP. Medical teams were composed by physicians and nurses from several disciplines.

Our medical emergency team (MET) is composed by an intensivist, a resident and a critical care nurse. During the pandemic, the MET was doubled during the surge and evaluated critical patients defining treatment limitations (i.e.: do not intubate order, DNI) together with the floor physician and the patient. A protocol was instituted for the use of helmet CPAP in COVID-19 patients who failed standard oxygen therapy (e-Figure 1 of the Additional File 1); failing was defined as one of the following during spontaneous breathing in non-rebreathing oxygen mask: SpO_2 <93%, respiratory rate >24 Breaths Per Minute (BPM), pCO_2 <35, thoraco-abdominal asynchronies.

CPAP delivery system

Our free-flow CPAP system relied on a Venturi flow generator connected to the oxygen wall port; a value of 60 L/min or above was the target for the fresh gas mixture flowing into the helmet.[21] FiO_2 was verified by a FiO_2 meter and adjusted based on oxygen saturation, while PEEP within the helmet was maintained by an adjustable mechanical valve. Helmet CPAP was managed by floor physicians and nurses; the most severe patients were referred directly to the MET and managed on the hospital floor until intubation was required, while the others were treated by non-intensivist physician and screened once a day by the MET for possible ICU admission.

Patients and data collection

Inclusion criteria were: respiratory failure treated with helmet following standard oxygen therapy; and a positive Sars-CoV-2 nasopharyngeal swabs (reverse transcription polymerase chain reaction). Exclusion criteria were: futility of medical treatment due to expected short term death independent of COVID-19 pneumonia.

The local online registry was developed with REDCap cloud 1.5 (Phase Inc). We collected data regarding past history; date of symptoms onset, hospital admission and helmet CPAP start (day 1); blood gas analysis before and after helmet CPAP start; data regarding the use of helmet CPAP and oxygenation for the first week (day 2-8); laboratory exams; chest x-ray examinations; need for intubation or ICU admission; treatment limitation decisions; hospital outcome. The proportion of missing data for each variable is reported in the e-Table 1 of the Additional File 1. An FiO_2 of 90% was considered for PaO_2/FiO_2 ratio calculation during non-rebreathing oxygen mask therapy. Helmet CPAP failure was defined as a composite outcome of death or ICU admission for intubation.

Safety of helmet CPAP treatment was evaluated by the presence of major adverse events, as recorded by the MET on the electronic medical records. Acute Respiratory Distress Syndrome (ARDS) was defined following the Berlin definition.[22]

Statistical analysis

Statistical analysis was performed using SPSS 17.0 (SPSS Inc). Data are reported as means ± standard deviation (SD) or median [25-75 percentiles]. Continuous variables were tested for normality by Shapiro-Wilk test. Comparisons between patients' groups were performed by Mann-Whitney or independent sample t-Test; comparisons within the same patient were performed by Wilcoxon or paired-sample t-Test, as appropriate. Comparisons between two categorical variables were performed by Fisher's Exact Test (two-by-two comparisons) or by Chi-Square Test (multiple classes). The analysis of helmet CPAP effects over PaO_2/FiO_2 ratio was conducted by repeated measures ANOVA, considering the PaO_2/FiO_2 before and after CPAP as within-subjects variables, and hypoxia severity class or treatment failure as between-subjects variable. The multivariate analyses to identify independent predictors of failure were performed by backward stepwise logistic regressions, considering CPAP failure as the dependent dichotomous

variable. We analyzed the treatment failure using the Kaplan–Meier approach with stratification for PaO_2/FiO_2 ratio assuming that patients discharged alive from hospital before 28 days were alive on that day; differences in time-curves were assessed by the Log-Rank test. A p-value lower than 0.05 was considered statistically significant.

Results

We enrolled in the study 306 consecutive patients (of the nearly 1500 COVID-19 treated) who failed oxygen mask therapy and underwent helmet CPAP treatment outside the ICU. Nearly 50% of the patients were younger than 65 years old ,PaO_2/FiO_2 ratio with standard oxygen therapy was lower than 150 in two-thirds of the patients (209/306). The majority of the patients had no (30%) or one (30%) comorbidity; about half of the enrolled patients had hypertension (Table 1).

Helmet CPAP treatment

After failure of standard oxygen therapy, helmet CPAP treatment was started with a median PEEP of 5 [5-10] cmH_2O and FiO_2 of 50% [50-90]. Helmet CPAP therapy led to a dramatic oxygenation improvement: PaO_2/FiO_2 ratio doubled from about 100 to 200 mmHg (P<0.001, Table 2). The incidence of severely hypoxic patients was markedly reduced by helmet CPAP (Figure 1a, P<0.001 by Chi-Square); the PaO_2/FiO_2 ratio improvement was more pronounced among more severely hypoxic patients (Figure 1b, P<0.001 for helmet CPAP effect and for its interaction with hypoxia severity class by RM Anova). A clinically significant reduction of respiratory rate was also present (from 28 [22-32] to 24 [20-29] BPM, P<0.001). After beginning of helmet CPAP, 71% of patients presented ARDS criteria (severe 9%; moderate 35%; mild 27%). Higher levels of C-Reactive Proteins were detected in patients whose hypoxaemia was not reverted by helmet CPAP treatment (P=0.009 by Anova, Figure 2). Considering the entire population, helmet CPAP was maintained for 6 [3-9] days with a median PEEP of 10 [7-10] cmH_2O and an FiO_2 of 65 [50-90] %. During the first two days after start of CPAP therapy, helmet was maintained in place for an average of 21 hours/day; from days three to five for an average of 19 hours/day. After the initial oxygenation improvement with helmet CPAP therapy, PaO_2/FiO_2 ratio remained steadily impaired during the first week (202 [128-284] mmHg).

Helmet CPAP failure occurred in 48% of the patients, mostly in patients who had a treatment limitation decision (71% vs. 31% in the full treatment group, P<0.001, Figure 3). CPAP failure was associated with several pre-existing factors, such as advanced age, number of comorbidities, and patient's frailty (Table 1). CPAP failure was strongly associated with worse gas exchange (Table 2, Figure 4), increased inflammatory markers, higher levels of serum lactate dehydrogenase and worse renal function (Table 1). Successful treatment was associated with a nearly double oxygenation response to helmet CPAP therapy as compared to failure (PaO_2/FiO_2 increase +96 vs. +53 mmHg, P=0.001); a PaO_2/FiO_2 increasing above 200 mmHg after positioning helmet CPAP (68% in the successful vs. 32% in the failure groups, P<0.001 by Chi-Square; P<0.001 by Log Rank, Figure 5); and a respiratory rate returning to clinically acceptable levels (22 vs. 28 BPM, P=0.007, Table 2).

A subgroup of patients (n=42) had a second evaluation on the first day of Helmet CPAP therapy. At the Receiving Operator Curve (ROC) curve analysis, the respiratory rate after few hours of helmet CPAP therapy was closely associated with CPAP success (AUC=0.802 [95% CI=0.66-0.94], *P*=0.001. A respiratory rate below 30 BPM showed 100% sensitivity for CPAP success; a respiratory rate above 24 showed 81% sensitivity and 76% specificity for CPAP failure.

The adoption of prone position sessions during helmet CPAP treatment was frequent (45%).

No major adverse event associated with the use of helmet CPAP (e.g. deaths of full treatment patients before intubation) was recorded by MET during the study period.

Full treatment patients

The majority of full treatment patients (122, 69%) did not require intubation and were successfully treated by helmet CPAP outside the ICU for 6 [4-9] days, with a PEEP of 10 [5-10] cmH_2O and a FiO_2 of 50 [35-80] %. Such patients were discharged from hospital after 14 [10-19] days. Full treatment patients requiring intubation (55, 31%) showed a higher heart rate on day one (92 [82-102] BPM vs. 80 [72-90], *P*<0.001). They were transferred to ICU for intubation after 4 [3-7] days of helmet CPAP treatment; in those patients, prone positioning was almost always attempted before intubation.

In the full treatment group, while PaO_2/FiO_2 ratio during standard oxygen therapy did not differ between the groups (*P*=0.208), helmet CPAP therapy led to a higher PaO_2/FiO_2 ratio in the success as compared to the failure group (257 [193-314] vs. 190 [131-259] *P*<0.001); this corresponded to a more pronounced response in oxygenation (PaO_2/FiO_2 increase +100 [45-162] mmHg vs. +51 [14-99], *P*=0.002). Among full treatment patients, a PaO_2/FiO_2 constantly above 150 mmHg during the first week was associates with a probability of recovery without intubation of 91% (*P*<0.001 by Fisher's Exact Test). Hospital mortality among full treatment patients was 13%.

DNI patients

A relevant number of patients (42%) had a treatment limitation decision (DNI). A DNI order was associated with age higher than 75 years old, a higher number of comorbidities and worse oxygenation both before and after helmet CPAP as compared to the full treatment group (*P*<0.001 for all). DNI order was strongly associated with helmet CPAP failure (which corresponds to mortality; *P*<0.001). However, a third of DNI patients (29%) had a favorable outcome with helmet CPAP treatment outside the ICU, despite a relevant oxygenation impairment on day one both with standard oxygen and with helmet CPAP therapy (PaO_2/FiO_2 ratio 104 [81-180] and 224 [151-319], respectively; *P*<0.001 for difference). Successful treatment was associated with younger age (*P*=0.025) and lower comorbidities (*P*=0.035).

Multivariate analysis

Factors included in the model, to predict CPAP failure were: age, sex, number of comorbidities, C-reactive protein (CRP), body temperature on day one, time to oxygen mask failure, PaO_2/FiO_2 ratio and $PaCO_2$ both during standard oxygen and helmet CPAP therapy. At the backward logistic regression analysis, helmet CPAP failure was independently associated with: CRP, time to oxygen mask failure, age, PaO_2/FiO_2 ratio collected during helmet CPAP treatment, number of comorbidities (Table 3). The other tested factors (sex, body temperature, PaO_2/FiO_2 ratio and $PaCO_2$ during standard oxygen treatment, $PaCO_2$ measured during CPAP) did not emerge as independent predictors of failure.

The results of a similar multivariate analysis including the PaO_2/FiO_2 ratio change in place of the PaO_2/FiO_2 ratio measured during helmet CPAP are reported in the e-Table 2 of the Additional File 1.

Discussion

In this observational study, we present the outcomes of helmet CPAP therapy for acute respiratory failure during the COVID-19 pandemic in a large Italian center. Helmet CPAP therapy outside ICU was feasible for several days (approximately one week), despite a severe gas exchange impairment. It was safely used to revert hypoxia and reduce respiratory distress on the hospital floor, representing an intermediate-level therapy to prevent intubation or ICU admission in nearly 70% of the full treatment patients. In DNI patients who failed standard oxygen therapy, a rescue trial with helmet CPAP represented a low resource strategy to prevent respiratory fatigue, exhaustion and arrest in about 30% of the patients.

In our hospitals, we have been using helmet CPAP since several years to apply PEEP during respiratory failure outside the ICU. Our approach to COVID-19 pneumonia, as in other types of pneumonia before the outbreak, is based on the rationale that PEEP and FiO_2 are the cornerstones of respiratory support when non-rebreathing oxygen mask fails and can be delivered non-invasively, safely and effectively on the hospital floor by helmet CPAP. Therefore, helmet CPAP represented a natural and valuable choice to face the pandemic and limit the need for intubation.

A free-flow Venturi system is simple to set-up and operate; a refresh course was provided to instruct floor nurses and physicians on the use of helmet CPAP, although most of the staff was already familiar with it. The treatment of hundreds of hypoxic patients simultaneously was possible thanks to the low cost of the kit and its ease of use. As in our previous experience, and taking advantage of a nurse-managed optimization bundle, helmet CPAP was well tolerated for many hours a day (almost continuously during the first days) and for many days afterwards[13], without relevant pressure ulcers.[21]

All the enrolled patients were in the need of upscale treatment, either for hypoxia or respiratory distress; however, intubating such a vast number of patients was not feasible. Helmet CPAP led to a marked and persisting oxygenation improvement in both full treatment and DNI patients, possibly indicating lung recruitment.[23] Ventilator effort was also reduced, as shown by lower respiratory rate shifting towards normal values after start of helmet CPAP therapy. As a consequence, we can speculate that patient self-inflicted lung injury was also reduced by helmet CPAP.

The criteria to define standard oxygen therapy failure were quite conservative but clinically acceptable, leading to a timely delivery of PEEP to hypoxic patients. We cannot exclude that few patients could have been treated with non-rebreathing mask for longer periods of time; however, the persisting oxygenation impairment over the study days (median PaO_2/FiO_2 ratio below 200) and the high FiO_2 need after start of helmet CPAP suggests worsening conditions, which would necessarily lead to upscaling therapy.

The vast majority of full treatment patients (about 70%) was successfully treated with helmet CPAP avoiding intubation, suggesting that a prolonged helmet CPAP treatment is effective for COVID-19 respiratory failure with a 24/7 availability of the MET. A PaO_2/FiO_2 ratio above 150 mmHg during helmet therapy was associated with a positive predictive value of 91% for treatment success, suggesting that intubation may be safely delayed in such patients. At the multivariate analysis, a lower PaO_2/FiO_2 value measured shortly after start of helmet CPAP was associated with failure, independent from age. Taken together, such data suggest that a helmet CPAP trial might provide useful information to the clinician about the evolution of the respiratory failure: simple markers such as a clear oxygenation improvement shortly after start of CPAP, a respiratory rate falling below 24 BPM within few hours, a PaO_2/FiO_2 persistently above 150 during the days, indicate that the patient can be treated effectively by helmet CPAP and possibly outside the ICU.

The benefits of helmet CPAP therapy were evident also in the DNI group. About 30% of DNI patients, who had no other treatment option, survived thanks to helmet CPAP as rescue treatment. The older age and the higher number of comorbidities suggest that preexisting conditions were the major culprits for failure in the DNI group, limiting the benefits of therapies focused on respiratory support such as helmet CPAP.

We acknowledge that we cannot draw definite conclusions about the timing and the effectiveness of CPAP therapy due to the observational nature of our data. However, a randomized trial comparing the use of CPAP vs. early intubation was not feasible during the pandemic for the shortage of ICU beds and might be considered unethical under different perspectives, due to the different invasiveness and risks for patients treated by CPAP as compared to intubation.

A different and widely used option to treat hypoxic patients unresponsive to non-rebreathing oxygen mask are high flow nasal cannula (HFNC).[24] We chose helmet CPAP as non-invasive respiratory support device for several reasons. First, HFNC provide a PEEP level much lower than CPAP, possibly representing a “low-dose” therapy for severely hypoxic patients. Second, the need for a dedicated heating and humidifying system with HFNC limited the use on a restricted number of patients, while active humidification may not be mandatory when spontaneously breathing a mixture of medical (dry) and ambient gas as within a Venturi based helmet CPAP. Third, the use of HFNC presented concerns for staff and environment contamination due to droplet spread, while helmet CPAP was the ideal device to limit droplet diffusion when using a HEPA filter on the outlet gas port.[13] Lastly, the MET and floor staff were already familiar with helmet CPAP, which has been used outside the ICU for many years in our hospital. Another limitation is that data were collected during a specific pandemic: adherence to hospital protocols was more difficult due to the increased clinical burden; some patients may have received intubation later

than usual due to ICU bed shortage; DNI orders may have been used more often than usual, denying ICU trials in elderly patients; data about patient comfort with the selected CPAP interface were not collected. All the presented factors may limit the generalizability of our data to patients affected by respiratory failure due to other etiologies. On the other side, the need to treat such a huge number of respiratory failure patients outside the ICU proved that helmet CPAP is a feasible and effective choice.

Conclusions

We showed that treatment of acute respiratory failure patients outside the ICU is feasible with helmet CPAP for many days, despite a persisting relevant degree of hypoxia. Treatment was also effective, leading to a marked oxygenation improvement; helmet CPAP therapy was associated with a good outcome in the vast majority of full treatment patients and an effective rescue for a limited but significant proportion of DNI patients.

List Of Abbreviations

ARDS acute respiratory distress syndrome

BPM breaths per minute

COVID-19 novel coronavirus disease

CPAP continuous positive airways pressure

CRP C-Reactive protein

DNI do not intubate

HFNC high flow nasal cannula

ICU intensive care unit

MET medical emergency team

PEEP positive end expiratory pressure

Declarations

Ethics approval and consent to participate Human participants were involved in this research; the study was conducted in accordance with the Declaration of Helsinki. Data were collected as part of the STORM study (Spallanzani Institute approval number 84/2020; NCT04424992). Patients' consent was waived.

Consent for publication N/A

Availability of data and materials The datasets used and analysed during the current study are available from the corresponding author after obtaining the approval of the Spallanzani Institute ethical committee.

Competing interests AC has a patent and received consultancy fees from Flowmeter for a topic possibly related to this article; GB has a patent and received consultancy fees from Flowmeter, lecturing fees from Dimar SRL and Intersugical SPA for a topic possibly related to this article; GF received lecturing fees from Dimar SRL. Other authors have no COI to disclose no conflict of interest.

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Authors' contributions AC GB and GF designed the study; AC AB RF LM PM MC GM AS BN EB RDS DI GC MGV AB AP PB DG GB contributed to data collection; AC had full access to all of the data in the study and takes responsibility for the integrity of the data; AC analyzed the data; AC and GB drafted the manuscript; all authors revised, read and approved the final manuscript.

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Tables

Table 1. Characteristics of study patients, comparing successful helmet CPAP treatment vs. failure

	All patients N=306	Successful helmet CPAP treatment N=159	Helmet CPAP failure N=147	*P* value
Age, years	67 [58-76]	62 [54-70]	71 [63-79]	<0.001
Sex male, n. (%)	236 (77)	121 (76)	115 (78)	0.685
Body Mass Index, kg/m^2	26 [24-30]	26 [24-30]	25 [24-30]	0.631
Any comorbidity, n. (%)	228 (74)	99 (62)	129 (88)	<0.001
Hypertension, n. (%)	159 (52)	69 (43)	90 (61)	0.002
Comorbidities, n.	1 [0-2]	1 [0-2]	2 [1-3]	<0.001
Clinical Frailty Scale	3 [2-4]	2 [2-3]	3 [2-5]	<0.001
Symptoms onset to Hospital admission, days	7 [4-10]	7 [5-10]	7 [4-10]	0.464
Hospital admission to oxygen therapy failure, days	1 [0-2]	1 [0-3]	0 [0-2]	0.001
Do not intubate (DNI) order, n (%)	129 (42)	37 (23)	92 (63)	<0.001
White Blood Cells, $n*10^3/\mu L$	7.38 [5.58-10.11]	7.03 [5.65-8.4]	7.71 [5.35-11.28]	0.052
Platelets, $n*10^3/\mu L$	202 [153-260]	213 [164-265]	183 [142-256]	0.027
C-Reactive Protein, mg/L	109 [50-172]	86 [39-131]	144 [67-207]	<0.001
Procalcitonin, ng/mL	0.29 [0.13-1.05]	0.2 [0.11-0.63]	0.44 [0.2-1.42]	0.001
Lactate Dehydrogenase, U/L	420 [332-524]	369 [313-477]	475 [375-589]	<0.001
Creatinine, mg/dL	1 [0.8-1.3]	1 [0.8-1.1]	1.1 [0.9-1.5]	<0.001
Urea, mg/dL	39 [28-61]	32 [25-44]	50 [33-84]	<0.001

Data regarding the study population (All patients), the subgroup of patients successfully treated by helmet CPAP (Successful helmet CPAP treatment) and the subgroup of patients failing the helmet CPAP treatment (either intubated or non-survivors, depending on their ceiling-of-care status) are reported in the table. The P value column refers to the comparison between the successful and the failing groups.

Table 2. Respiratory parameters collected with standard oxygen therapy and shortly after start of helmet CPAP

	All patients Standard Oxygen N=306	*P* value (O_2 vs. CPAP)	All patients Helmet CPAP N=306	Successful Helmet CPAP treatment N=159	Helmet CPAP failure N=147	*P* value (success vs. failure)
PaO_2/FiO_2 ratio, mmHg	103 [79-176]	<0.001	202 [146-284]	252 [186-316]	166 [114-243]	<0.001
O_2 saturation, %	95 [91-97]	<0.001	98 [96-99]	99 [97-99]	97 [95-99]	<0.001
$PaCO_2$, mmHg	33 [30-36]	0.011	33 [30.5-36]	33.2 [31-36.2]	32.5 [30-35.2]	0.091
Resp Rate, BPM	28 [22-32]	<0.001	24 [20-29]	22 [19-25]	28 [20-32]	0.007
PEEP, cm H_2O			5 [5-10]	5 [5-8]	5 [5-10]	0.010
FiO_2, %			50 [50-90]	50 [50-70]	60 [50-100]	<0.001
PaO_2/FiO_2 ratio increase with CPAP, mmHg			83 [28-154]	96 [45-176]	53 [18-115]	<0.001
ARDS patients, n (%)			178 (71)	78 (62)	100 (79)	0.006

The *P* value (O_2 vs. CPAP) column refers to the statistical comparison of the same patients before and after helmet CPAP therapy; the *P* value (success vs. failure) column refers to the comparison of the values measured after beginning of helmet CPAP in the success and the failure subgroups.

BPM: breaths per minute; PEEP: positive end expiratory pressure; CPAP: continuous positive airway pressure; ARDS: acute respiratory distress syndrome

Table 3. Multivariate analysis of independent predictors of helmet CPAP failure

Factor[a]	*P* value	Odds Ratio [95% C.I.]
C-Reactive Protein, mg/L	0.001	1.006 [1.003-1.010]
Hospital admission to oxygen therapy failure, days	0.001	0.775 [0.661-0.908]
Age, years	0.002	1.054 [1.020-1.089]
PaO_2/FiO_2 ratio (helmet CPAP), mmHg	0.003	0.995 [0.991-0.998]
Comorbidities, n.	0.005	1.582 [1.147-2.182]

[a] factors entered in the backward regression model and removed due to lack of statistical significance ($P>0.05$): sex, body temperature, PaO_2/FiO_2 ratio and $PaCO_2$ during standard oxygen treatment, $PaCO_2$ measured during CPAP. Age, number of comorbidities, C-reactive protein levels, time to standard oxygen therapy failure, and the PaO_2/FiO_2 ratio measured after start of helmet CPAP were independent predictors of non-invasive treatment failure. CPAP: continuous positive airway pressure