Helmet CPAP to treat hypoxic pneumonia outside the ICU: an observational study during the COVID-19 outbreak

Andrea Coppadoro

    ASST di Monza: Azienda Socio Sanitaria Territoriale di Monza

Annalisa Benini

    ASST di Monza: Azienda Socio Sanitaria Territoriale di Monza

Robert Fruscio

    University of Milano−Bicocca: Universita degli Studi di Milano-Bicocca

Luisa Verga

    ASST di Monza: Azienda Socio Sanitaria Territoriale di Monza

Paolo Mazzola

    University of Milano−Bicocca: Universita degli Studi di Milano-Bicocca

Giuseppe Bellelli

    University of Milano−Bicocca: Universita degli Studi di Milano-Bicocca

Marco Carbone

    University of Milano−Bicocca: Universita degli Studi di Milano-Bicocca

Giacomo Mulinacci

    University of Milano−Bicocca: Universita degli Studi di Milano-Bicocca

Alessandro Soria

    ASST di Monza: Azienda Socio Sanitaria Territoriale di Monza

Beatrice Noe'

    University of Milano−Bicocca: Universita degli Studi di Milano-Bicocca

Eduardo Beck

    ASST di Monza: Azienda Socio Sanitaria Territoriale di Monza

Riccardo Di Sciacca

    ASST di Monza: Azienda Socio Sanitaria Territoriale di Monza

Davide Ippolito

    ASST di Monza: Azienda Socio Sanitaria Territoriale di Monza

Giuseppe Citerio

    University of Milano−Bicocca: Universita degli Studi di Milano-Bicocca

Grazia Valsecchi

    University of Milano−Bicocca: Universita degli Studi di Milano-Bicocca

Andrea Biondi

University of Milano–Bicocca: Universita degli Studi di Milano-Bicocca

Alberto Pesci

University of Milano–Bicocca: Universita degli Studi di Milano-Bicocca

Paolo Bonfanti

University of Milano–Bicocca: Universita degli Studi di Milano-Bicocca

Davide Gaudesi

University of Milano–Bicocca: Universita degli Studi di Milano-Bicocca

Giacomo Bellani (✉ giacomo.bellani1@unimib.it)

University of Milan Bicocca   https://orcid.org/0000-0002-3089-205X

Giuseppe Foti

University of Milano–Bicocca: Universita degli Studi di Milano-Bicocca

---

Research

Abstract

Background: Respiratory failure due to COVID-19 pneumonia is associated with high mortality and may overwhelm health care systems, 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 gas exchange impairment. 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, thereafter. 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 28% 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, $P<0.001$). C-Reactive Protein, time to oxygen mask failure, age, PaO_2/FiO_2 during CPAP, number of comorbidities were independently associated with CPAP failure. 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 persistent impairment in gas exchange. It was used, without escalating to intubation, in the majority of full treatment patients after standard oxygen therapy failed. 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, an overwhelming number of patients suffering from hypoxemic respiratory failure presented to hospitals' emergency rooms, burdening the health system to an unexpected extent. To face such a number of critically ill 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$_2$O) 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] a topic on which a vigorous debate is ongoing.[9]

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.[10, 11] 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.[12] When treating COVID-19 affected patients, the use of helmets might bear the additional advantage of reducing virus environment contamination.[13, 14] Recent reports suggest that helmet CPAP can be effective for COVID-19 treatment,[15-17] possibly combined with prone or lateral position.[18-20] 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.[21]

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 of COVID-19 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; ICU beds were increased up to one-hundred during the surge. Several medical and surgical wards were converted in COVID-19 wards, capable of applying non-invasive CPAP. Ward 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); failure of standard oxygen therapy 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 mmHg, thoraco-abdominal asynchronies.

CPAP delivery system

Our free-flow CPAP system (e-Figure 2) 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.[22] FiO_2 was verified by a FiO_2 meter and adjusted based on oxygen saturation, while PEEP (i.e. CPAP level) 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. Intra-venous sedation was not used in the wards during helmet CPAP treatment, except for palliative care of terminal patients; some patients might have received oral benzodiazepines for relief of anxiety.

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 and frailty;[23] date of symptoms onset, hospital admission and helmet CPAP start (day 1); blood gas analysis before and after (normally between one and two hours) 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 [24], albeit this estimation might lack of precision, particularly at higher values of minute ventilation.[25] Helmet CPAP failure was defined as a composite outcome of death or ICU admission for intubation. Albeit criteria for DNI decision or intubation were not protocolized, the MET was composed by a relatively small number of clinicians who shared decisions whenever possible and who met periodically to re-evaluate clinical strategies, decisions taken, controversies with colleagues, hence behaving consistently.

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.[26]

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 severity of impairment in gas exchange or treatment failure as between-subjects variable. The multivariate analyses to identify independent factors associated with failure were performed by backward 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. The level of significance was 0.05 (two-tailed test) unless otherwise specified to account for multiple comparisons (Bonferroni correction).

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 and 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 median delay between the two arterial blood gases samplings (with standard oxygen mask and helmet CPAP) was rather short (median 3.5 [2-6] hours), albeit we did not collect the exact timing at which CPAP was initiated between these two. The incidence of severe gas exchange impairment 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 patients who showed a more pronounced gas exchange impairment (Figure 1b, $P<0.001$ for helmet CPAP effect and for its interaction with PaO_2/FiO_2 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 gas exchange impairment was not improved 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. Patients could eat and drink during the CPAP breaks. 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 (72% 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, a data which was missing for 120 patients (Table 1). CPAP failure was strongly associated with worse gas exchange (Table 3, Figure 4), increased inflammatory markers, higher levels of serum lactate dehydrogenase and worse renal function (Table 1). Successful treatment with CPAP (i.e.: hospital discharge without intubation) 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, $P=0.001$). Helmet CPAP failure probability showed a different pattern if patients were stratified according to PaO_2/FiO_2 ratio measured either during standard oxygen or during helmet CPAP (figure 5). 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) were re-evaluated by the MET, of CPAP, on the first day of helmet CPAP therapy a few hours after initiation. 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$_2$O and a FiO$_2$ of 50 [35-80] %. Such patients were discharged from hospital after 14 [10-19] days. Patients requiring intubation (54, 31%) showed a higher heart rate on day one than those who did not (119, 68%) (92 [83-102] 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.

While PaO_2/FiO_2 ratio during standard oxygen therapy did not differ between the success and failure groups ($P=0.280$), helmet CPAP therapy led to a higher PaO_2/FiO_2 ratio in the success as compared to the failure group at the first measurement (257 [193-314] vs. 193 [133-259] $P<0.001$); this corresponded to a more pronounced response in oxygenation (PaO_2/FiO_2 increase +100 [45-162] mmHg vs. +51 [12-99], $P=0.003$). Among full treatment patients, a PaO_2/FiO_2 constantly above 150 mmHg during the first week was associated with a probability of recovery without intubation of 91% ($P<0.001$ by Fisher's Exact Test). Hospital mortality among full treatment patients was 12.5% (22/154). All deaths occurred after ICU

admission; patients who eventually died spent a shorter period on CPAP as compared to ICU survivors (4[2-5] vs. 5 [4-8] days, p=0.05), probably due to a more severe and aggressive disease.

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). A DNI order was strongly associated with helmet CPAP failure (which corresponds to mortality; P<0.001). However, more than a quarter of DNI patients (28%) 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 among DNI patients was associated with younger age (P=0.023) and lower comorbidities (P=0.03).

Multivariate analysis

Factors included in the model, to predict CPAP failure were: age, sex, number of comorbidities, C-reactive protein, body temperature on day one, time to oxygen mask failure, PaO_2/FiO_2 ratio and $PaCO_2$ both during standard oxygen and at the first measurement during helmet CPAP. At the backward logistic regression analysis, C-reactive protein, time to oxygen mask failure, age, PaO_2/FiO_2 ratio collected during helmet CPAP treatment and number of comorbidities were independently associated with helmet CPAP failure (Table 4). 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 list of factors entered in the backward analysis is reported in the e-Table 2 of the Additional File 1. The results of a similar multivariate analysis including the PaO_2/FiO_2 ratio change due to helmet CPAP in place of the PaO_2/FiO_2 ratio measured during helmet CPAP are reported in the e-Table 3 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 improve oxygenation and reduce respiratory distress (indirectly assessed, in a subset of patients, by respiratory rate) 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 last treatment option with low invasiveness, which might have contributed to the observed 30 % survival.

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 personnel, allowing us to rapidly escalate the treatment to hundreds of hypoxemic patients. In comparison with "classical" Pressure Support, the use of free flow helmet CPAP has the main advantages of not requiring a ventilator (whose shortage represented a major issue during pandemics) and not presenting any issue of patient-ventilator synchrony, even in the presence of leaks, elevated respiratory rate, patient movement and so forth. Taking advantage of a nurse-managed optimization bundle, helmet CPAP was well tolerated for many hours a day (almost continuously during the first days)[14], without relevant pressure ulcers.[22]

All the enrolled patients were in the need of upscale treatment, either for hypoxaemia or respiratory distress; however, it was crucial to carefully select and minimize the number of patients undergoing intubation and to have a safe bridge for those in whom intubation had to be postponed for logistical reasons. Helmet CPAP led to a marked and persistent oxygenation improvement in both full treatment and DNI patients, possibly indicating lung recruitment.[27] Ventilator effort was also reduced, as shown by lower respiratory rate shifting towards normal values after start of helmet CPAP therapy. Unfortunately, the way in which clinicians measured respiratory rate was not specified a-priori, standardized or even recorded and might be affected by several limitations.[28] Hence, helmet CPAP might have reduced the so-called patient self-inflicted lung injury, whose putative existence and clinical is a matter of debate.[9, 29] In this respect it must be also noted that a limitation inherent to the use of helmet is the inability of monitoring tidal volume, an important parameter to predict NIV failure.[30]

The criteria to define standard oxygen therapy failure were quite conservative, leading to an early delivery of PEEP to hypoxemic patients. We cannot exclude that few patients could have been treated with non-rebreathing mask for longer periods of time; however, the persistent 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 escalate therapy.

The vast majority of full treatment patients (about 70%) was successfully treated with helmet CPAP without escalating to 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. 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. In a previous trial, Patel's et al. enrolled full treatment patients needing CPAP and compared helmet with face mask, showing a much lower need for intubation with helmets (18% vs. 61%).[10] The 31% failure rate recorded in our population is slightly higher than Patel's trial; possible explanations for the higher failure recorded in our population may be 1) the lack of a proven therapy for COVID-19 patients (either etiological or supportive, since steroids were not consistently used in March, 2020) and 2) the inability of replicating in the hospital ward the typical ICU tight monitoring for a vast number of patients.

The benefits of helmet CPAP therapy were evident also in the DNI group, where this strategy might have contributed to the 30% survival of DNI patients, who had no other treatment option for respiratory failure. 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 hypoxemic patients unresponsive to non-rebreathing oxygen mask are high flow nasal cannula (HFNC).[31] 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 patients affected by severe gas exchange impairment. 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[14]. 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.

A limitation of our approach is therefore that the failure rate might not be the same if this technique was applied in other contexts, with difference experience, protocols or patients selection. 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. Finally, the threshold and predictive values which we report (e.g. for PaO2/FiO2 and respiratory rate) were not

evaluated prospectively. 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 persistent relevant degree of gas exchange impairment. 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

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.

References

1. Grasselli G, Pesenti A, Cecconi M. Critical Care Utilization for the COVID-19 Outbreak in Lombardy, Italy: Early Experience and Forecast During an Emergency Response. JAMA. 2020; doi: 10.1001/jama.2020.4031.

2. Bellani G, Laffey JG, Pham T, Madotto F, Fan E, Brochard L et al. Noninvasive Ventilation of Patients with Acute Respiratory Distress Syndrome. Insights from the LUNG SAFE Study. Am J Respir Crit Care Med. 2017;195:67-77.

3. Cabrini L, Landoni G, Oriani A, Plumari VP, Nobile L, Greco M et al. Noninvasive ventilation and survival in acute care settings: a comprehensive systematic review and metaanalysis of randomized controlled trials. Crit Care Med. 2015;43:880-888.

4. Cosentini R, Brambilla AM, Aliberti S, Bignamini A, Nava S, Maffei A et al. Helmet continuous positive airway pressure vs oxygen therapy to improve oxygenation in community-acquired pneumonia: a randomized, controlled trial. Chest. 2010;138:114-120.

5. Brambilla AM, Aliberti S, Prina E, Nicoli F, Del Forno M, Nava S et al. Helmet CPAP vs. oxygen therapy in severe hypoxemic respiratory failure due to pneumonia. Intensive Care Med. 2014;40:942-949.

6. Alhazzani W, Moller MH, Arabi YM, Loeb M, Gong MN, Fan E et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med. 2020;46:854-887.

7. 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;46:1099-1102.

8. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2020;201:1299-1300.

9. Tobin MJ, Laghi F, Jubran A. P-SILI is not justification for intubation of COVID-19 patients. Ann Intensive Care. 2020;10:105.

10. Patel BK, Wolfe KS, Pohlman AS, Hall JB, Kress JP. Effect of Noninvasive Ventilation Delivered by Helmet vs Face Mask on the Rate of Endotracheal Intubation in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. JAMA. 2016;315:2435-2441.

11. Ferreyro BL, Angriman F, Munshi L, Del Sorbo L, Ferguson ND, Rochwerg B et al. Association of Noninvasive Oxygenation Strategies With All-Cause Mortality in Adults With Acute Hypoxemic Respiratory Failure: A Systematic Review and Meta-analysis. JAMA. 2020; doi: 10.1001/jama.2020.9524.

12. Antonelli M, Conti G, Pelosi P, Gregoretti C, Pennisi MA, Costa R et al. New treatment of acute hypoxemic respiratory failure: noninvasive pressure support ventilation delivered by helmet—a pilot controlled trial. Crit Care Med. 2002;30:602-608.

13. Vitacca M, Nava S, Santus P, Harari S. Early consensus management for non-ICU acute respiratory failure SARS-CoV-2 emergency in Italy: from ward to trenches. Eur Respir J. 2020;55 doi: 10.1183/13993003.00632-2020.

14. Lucchini A, Giani M, Isgro S, Rona R, Foti G. The "helmet bundle" in COVID-19 patients undergoing non invasive ventilation. Intensive Crit Care Nurs. 2020; doi: 10.1016/j.iccn.2020.102859.

15. Duca A, Memaj I, Zanardi F, Preti C, Alesi A, Della Bella L et al. Severity of respiratory failure and outcome of patients needing a ventilatory support in the Emergency Department during Italian novel coronavirus SARS-CoV2 outbreak: Preliminary data on the role of Helmet CPAP and Non-Invasive Positive Pressure Ventilation. EClinicalMedicine. 2020; doi: 10.1016/j.eclinm.2020.100419.

16. Rali AS, Howard C, Miller R, Morgan CK, Mejia D, Sabo J et al. Helmet CPAP revisited in COVID-19 pneumonia: A case series. Can J Respir Ther. 2020;56:32-34.

17. Armirfarzan H, Shanahan JL, Schuman R, Leissner KB. Helmet CPAP: how an unfamiliar respiratory tool is moving into treatment options during COVID-19 in the US. Ther Adv Respir Dis. 2020; doi: 10.1177/1753466620951032.

18. Longhini F, Bruni A, Garofalo E, Navalesi P, Grasselli G, Cosentini R et al. Helmet continuous positive airway pressure and prone positioning: A proposal for an early management of COVID-19 patients. Pulmonology. 2020;26:186-191.

19. Coppo A, Bellani G, Winterton D, Di Pierro M, Soria A, Faverio P et al. Feasibility and physiological effects of prone positioning in non-intubated patients with acute respiratory failure due to COVID-19 (PRON-COVID): a prospective cohort study. Lancet Respir Med. 2020;8:765-774.

20. Retucci M, Aliberti S, Ceruti C, Santambrogio M, Tammaro S, Cuccarini F et al. Prone and Lateral Positioning in Spontaneously Breathing Patients With COVID-19 Pneumonia Undergoing Noninvasive Helmet CPAP Treatment. Chest. 2020; doi: 10.1016/j.chest.2020.07.006.

21. Aliberti S, Radovanovic D, Billi F, Sotgiu G, Costanzo M, Pilocane T et al. Helmet CPAP treatment in patients with COVID-19 pneumonia: a multicenter, cohort study. Eur Respir J. 2020; doi: 10.1183/13993003.01935-2020.

22. Bellani G, Patroniti N, Greco M, Foti G, Pesenti A. The use of helmets to deliver non-invasive continuous positive airway pressure in hypoxemic acute respiratory failure. Minerva Anestesiol.

2008;74:651-656.

23. Rockwood K, Theou O. Using the Clinical Frailty Scale in Allocating Scarce Health Care Resources. Can Geriatr J. 2020;23:210-215

24. Instructions to complete the CRF for the EPIC II study, last accessed on 2020 October 28th [https://www.intensive.org/epic2/Documents/Estimation%20of%20PO2%20and%20FiO2.pdf]

25. Farias E RL, Zidulka A. Delivery of high inspired oxygen by face mask. J Crit Care. 1991;6:119-124

26. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307:2526-2533.

27. Mauri T, Spinelli E, Scotti E, Colussi G, Basile MC, Crotti S et al. Potential for Lung Recruitment and Ventilation-Perfusion Mismatch in Patients With the Acute Respiratory Distress Syndrome From Coronavirus Disease 2019. Crit Care Med. 2020;48:1129-1134.

28. Krieger B, Feinerman D, Zaron A, Bizousky F. Continuous noninvasive monitoring of respiratory rate in critically ill patients. Chest. 1986;90:632-634.

29. Tobin MJ, Laghi F, Jubran A. Caution about early intubation and mechanical ventilation in COVID-19. Ann Intensive Care. 2020; doi: 10.1186/s13613-020-00692-6.

30. Carteaux G, Millan-Guilarte T, De Prost N, Razazi K, Abid S, Thille AW et al. Failure of Noninvasive Ventilation for De Novo Acute Hypoxemic Respiratory Failure: Role of Tidal Volume. Crit Care Med. 2016;44:282-290.

31. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015;372:2185-2196.

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 (%)	130 (42)	37 (23)	93 (63)	<0.001*
White Blood Cells, n*10^3/µL	7.38 [5.58-10.11]	7.03 [5.65-8.4]	7.71 [5.35-11.28]	0.052
Platelets, n*10^3/µL	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*

Univariate analysis of the association of relevant characteristics with CPAP failure. 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. Asterisks (*) indicates persistence of statistically significant differences after Bonferroni correction for multiple comparisons (p<0.003).

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

	Standard Oxygen N=306	Helmet CPAP N=306	P value
PaO_2/FiO_2 ratio, mmHg	103 [79-176]	202 [146-284]	<0.001*
O_2 saturation, %	95 [91-97]	98 [96-99]	<0.001*
$PaCO_2$, mmHg	33 [30-36]	33 [30.5-36]	0.011*
Resp Rate, BPM	28 [22-32]	24 [20-29]	<0.001*

BPM: breaths per minute; PEEP: positive end expiratory pressure; CPAP: continuous positive airway pressure; ARDS: acute respiratory distress syndrome. Asterisks (*) indicates persistence of statistically significant differences after Bonferroni correction for multiple comparisons (p<0.012).

Table 3. Respiratory parameters collected shortly after start of helmet CPAP in success vs failures

	All patients Helmet CPAP N=306	Successful Helmet CPAP treatment N=159	Helmet CPAP failure N=147	P value
PaO_2/FiO_2 ratio, mmHg	202 [146-284]	252 [186-316]	166 [114-243]	<0.001*
$PaCO_2$, mmHg	33 [30.5-36]	33.2 [31-36.2]	32.5 [30-35.2]	0.091
Resp Rate, BPM	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*
PaO_2/FiO_2 ratio increase with CPAP, mmHg	83 [28-154]	96 [45-176]	53 [18-115]	<0.001*
ARDS diagnosis, n (%)	178 (71)	78 (62)	100 (79)	0.006*

Univariate analysis of the association of respiratory parameters collected shortly after CPAP start with CPAP failure during hospital stay. BPM: breaths per minute; PEEP: positive end expiratory pressure; CPAP: continuous positive airway pressure; ARDS: acute respiratory distress syndrome. Asterisks (*) indicates statistically significant differences after Bonferroni correction for multiple comparisons (p<0.009)

Table 4. Multivariate analysis of factors associated with 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. C-reactive protein, time to oxygen mask

failure, age, PaO_2/FiO_2 ratio collected during helmet CPAP treatment and number of comorbidities were independently associated with helmet CPAP failure. CPAP: continuous positive airway pressure