Helmet CPAP treatment in patients with COVID-19 pneumonia: a multicentre cohort study

To the Editor:

Patients with coronavirus disease 2019 (COVID-19) pneumonia can develop hypoxaemic acute respiratory failure (hARF) with the need for positive end-expiratory pressure (PEEP). The administration of continuous positive airway pressure (CPAP) through a helmet improves oxygenation and avoids intubation [1, 2]. A European consensus document suggests that helmet CPAP should be the first therapeutic choice for hARF caused by COVID-19 pneumonia, mainly for minimising aerosol generation [3–5]. However, recommendations are based on experts' opinion and consider only evidence obtained in critically ill COVID-19 patients [3]. The Surviving Sepsis Campaign does not recommend the administration of CPAP for the initial management of severe COVID-19 [6].

In order to evaluate outcomes of COVID-19 patients with pneumonia-related hARF undergoing CPAP treatment, a multicentre, observational, prospective study was conducted between 7 March 2020 and 21 April 2020 in three high-dependency units (HDU) at two hospitals in Milan, Italy. Adults (aged ⩾18 years) with hARF secondary to community-acquired COVID-19 pneumonia undergoing helmet CPAP treatment were consecutively recruited. Indications for helmet CPAP included all of the following: a diagnosis of pneumonia as the only cause of hARF and an arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}) ratio <300 evaluated during oxygen therapy supplied for at least 30 min through either a Venturi mask (F_{IO_2} of at least 0.50) or reservoir mask. CPAP was delivered through high-flow generators (VitalSigns Inc; 90–140 L·min^{-1}; MYO 3133A, Pulmodyne) using a helmet (StarMed) as interface with a PEEP valve (VitalSigns). The presence of other causes of hARF were excluded by clinical evaluation. Patients with at least one of the following criteria were excluded: need for immediate intubation; Glasgow Coma Scale <15; respiratory acidosis; systolic blood pressure (SBP) <90 mmHg despite fluid resuscitation and/or use of vasopressors; swallowing disturbance with increasing risk of aspiration pneumonia; and inability to protect the airways. The Ethical Committees of the two hospitals approved the study (No. 345/2020 and No. 17263/2020). Demographic, epidemiological, clinical, and laboratory data were recorded at admission. Arterial blood gas analysis and vital signs were recorded before CPAP, and within 6 h, on day 3 and day 7 after CPAP initiation. Lung recruitability during CPAP treatment was defined as an increase of P_{aO_2}/F_{IO_2} ratio of at least 30% from oxygen therapy (baseline) to CPAP treatment (within 6 h). Severe pneumonia on admission was defined according to latest American Thoracic Society/Infectious Diseases Society of America guidelines [7]. Patients were followed up to either 30-days or hospital discharge if still hospitalised at 30 day from HDU admission. The primary outcome was CPAP failure defined as the occurrence of either intubation or death due to any cause during HDU stay. According to local standard operating procedures, indication for intubation included the presence of either at least 1 major or at least two minor criteria lasting for ⩾1 h. Major criteria were: respiratory arrest; respiratory pause with unconsciousness; severe haemodynamic instability (*i.e.* SBP <90 mmHg instead of adequate volume resuscitation); and intolerance to helmet CPAP leading to discontinuation of the device. Minor criteria were: reduction of ⩾30% of basal P_{aO_2}/F_{IO_2} ratio; P_{aO_2}/F_{IO_2} ratio <100; 20% increase of arterial carbon dioxide tension if basal arterial carbon dioxide tension was ⩾40 mmHg; worsening of alertness; new onset or persistent respiratory distress; oxygen saturation measured by pulse oximetry (S_{pO_2}) <90%; and exhaustion. Achievement of the criteria did not automatically imply intubation of the patient, since this decision was based on a multidisciplinary discussion among the attending physician, the senior

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attending physician and the critical care physician. Secondary outcomes included the weaning from CPAP to oxygen therapy (CPAP success), all-cause in-hospital and 30-day mortality. A Do-Not-Intubate (DNI) order was defined as the decision of the attending physician in charge (after discussion with the critical care physician) to withheld intubation and to use CPAP as "ceiling" treatment considering the patient's characteristics (*e.g.* extremely poor functional status prior on admission, very low predicted probability of hospital survival, patient's own opinion when reliable, frailty score and comorbidities). Weaning from helmet CPAP was standardised across the three HDUs. Patients on helmet CPAP who did not show signs of respiratory distress (*e.g.* respiratory rate <25 breaths·min$_{-1}$) and maintained a S_{pO_2} >94% with a F_{IO_2} <50% and a PEEP ⩽5 cmH_2O underwent a weaning trial. Patients maintaining a P_{aO_2}/F_{IO_2} ratio >250 on Venturi mask with a F_{IO_2} <40% for at least 24 h were considered successfully weaned from helmet CPAP. Qualitative and quantitative variables were summarised with frequencies (absolute and relative) and central tendency (means and medians) and variability (standard deviations and interquartile ranges) indicators, depending on their parametric distribution. A Chi-squared or Fisher exact test was computed for qualitative variables; Student *t*-test or Mann–Whitney was used for quantitative variables with a parametric or non-parametric distribution, respectively. A Cox proportional hazards regression analysis was carried out to assess the relationship between the composite primary outcome and independent variables. No specific computations were carried out. All the individuals potentially fitting the study selection criteria were recruited when admitted at the two hospitals in Milan. A two-tailed p-value <0.05 was considered statistically significant. Statistical computations were performed with STATA version 16 (StatsCorp, College Station, TX, USA).

A total of 157 patients (74.5% males, median (IQR) age: 64 (55–75) years) with hARF (median (IQR) P_{aO_2}/F_{IO_2} ratio 142.9 (96.7–203.2)) underwent helmet CPAP with an initial median (IQR) F_{IO_2} of 0.6 (0.5–0.6) and mean±SD PEEP of 10.8±2.3 cmH_2O (table 1). The most prevalent comorbidities were arterial hypertension (44.0%), diabetes (22.9%), ischaemic cardiac disease (17.2%) and chronic arrhythmia (10.8%). Hypoxaemia generally improved when CPAP treatment was initiated: median (IQR) values of P_{aO_2}/F_{IO_2} ratio at baseline on oxygen therapy (142.9 (96.7–203.2)) significantly improved when helmet CPAP was used after 6 h (205.6 (140.0–271.1), p<0.0001). However, an increase of at least 30% in P_{aO_2}/F_{IO_2} ratio during helmet CPAP application in comparison to oxygen therapy was found only in 52% of the population. Median (IQR) duration of helmet CPAP treatment was 6 (3–10) days. Only four patients discontinued helmet CPAP because of intolerance. No patients were lost during follow-up. CPAP failure was observed in 70 (44.6%) patients: 34 (21.7%) were intubated and 36 (22.9%) died during the HDU stay. 87 (55.4%) patients improved during the HDU stay, weaned to oxygen therapy and transferred to the general ward. No patients were intubated during the first hours after CPAP initiation or under high emergency conditions (*e.g.* cardiac arrest). Among those who died in HDU, pneumonia-related deaths were detected in 26 patients, while non-pneumonia related in 10 patients, including pulmonary embolisms (n=5), end-stage renal failure (n=2), cerebrovascular accident (n=1), end-stage heart failure (n=1) and septic shock (n=1). Among the 34 patients who were intubated in HDU and transferred to the ICU, nine (26.5%) died. A total of 65 (41.4%) patients had a DNI status on HDU admission: 36 died and 29 survived. At the multivariable analysis (adjusted for sex, age, severe community-acquired pneumonia, interleukin-6, and $\Delta P_{aO_2}/F_{IO_2}$ ratio ⩾30%), CPAP failure was associated with the severity of pneumonia on admission (HR (95%CI) 2.9 (1.3–6.2), p=0.009) and higher baseline values of interleukin-6 (HR (95%CI) 1.0 (1.0–1.0), p<0.009). The all-cause in-hospital and 30-day mortality rates were 28.7% and 28.0%, respectively.

The rate of CPAP failure (either intubation or death) in COVID-19 patients seems to be higher in our study compared with the one recently reported in a multicentre, observational study which enrolled non-COVID-19 pneumonia patients with comparable severity of hARF (44.6% *versus* 23%) [8]. Both intubation (21.7% *versus* 11%) and mortality (22.9% *versus* 12%) rates were also higher in COVID-19 pneumonia than non-COVID-19 pneumonia patients [8]. This finding can be explained by the complex phenomena behind the occurrence of the respiratory failure experienced by COVID-19 patients, which is often paralleled by local vascular micro-thrombosis, and, more importantly, by the absence of a treatment of proven efficacy [9]. Nevertheless, the overall mortality rate of our cohort was comparable to that recently reported in ICU patients [10]. A total of 55.4% of our patients with a median P_{aO_2}/F_{IO_2} ratio of 136 and treated with helmet CPAP avoided intubation, and, then, were successfully weaned to oxygen therapy. Unfortunately, prognostic criteria which can discriminate responders to CPAP therapy at HDU admission are still lacking. Finally, a French study enrolled 38 COVID patients with acute respiratory failure and suggested that CPAP seems to avoid intubation especially in DNI patients [11]. It is difficult to compare our results with those by Oranger *et al.* [11] for different reasons, including the different intervention (Boussignac and oro-nasal CPAP *versus* helmet CPAP), unclear severity of respiratory failure (only P_{aO_2} was reported), inclusion of patients needing oxygen >6 L·min^{-1} to maintain an S_{pO_2} >92%, which represents a selection bias (increase of the number of milder patients), and the absence of a mortality rate reported in the CPAP arm.

TABLE 1 Baseline characteristics, continuous positive airway pressure (CPAP) treatment and outcomes of the study population according to CPAP failure or success

	CPAP success	CPAP failure	p-value
Subjects n	87	70	
Demographics			
Males	60 (69.0)	57 (81.4)	0.08
Age years	66 (56–75)	60 (51–72)	0.08
>65 years	45 (51.7)	26 (27.1)	0.07
>75 years	20 (23.0)	15 (21.4)	0.82
BMI	27.4 (25.1–30.2)	27.5 (23.7–29.3)	0.39
Obesity (BMI ⩾30 kg·m^{-2})	16 (25.4)	13 (24.1)	0.87
Current/former smoker	17 (19.5)	10 (14.3)	0.39
Comorbidities			
Any cardiovascular disease	49 (56.3)	32 (45.7)	0.19
Hypertension	41 (47.1)	28 (40.0)	0.37
Diabetes	24 (27.6)	12 (17.1)	0.12
Ischaemic cardiac disease	19 (21.8)	8 (11.4)	0.09
Chronic arrhythmia	7 (8.1)	10 (14.3)	0.21
Cerebrovascular disease	9 (10.3)	4 (5.7)	0.39
Immunosuppression	8 (9.2)	3 (4.3)	0.35
COPD	7 (8.1)	3 (4.3)	0.51
Chronic renal failure	6 (6.9)	3 (4.3)	0.73
Liver disease	5 (5.8)	4 (5.7)	1.00
Asthma	1 (1.29	2 (2.9)	0.59
Radiology			
Consolidation on chest radiograph	66 (75.9)	58 (82.3)	0.29
Pleural effusion	15 (17.2)	11 (15.7)	0.80
Pharmacological treatment			
Treatment with immunomodulators			
None	56 (64.4)	42 (60.0)	0.74
Anakinra	26 (29.9)	22 (31.4)	
Tocilizumab	5 (5.8)	6 (8.6)	
Hydroxychloroquine	84 (96.6)	68 (97.1)	0.83
Lopinavir/ritonavir	48 (55.2)	37 (52.9)	0.77
Remdesivir	2 (2.3)	3 (4.3)	0.66
Endovenous steroids	37 (42.5)	35 (50.0)	0.42
Antibiotics	84 (96.6)	66 (94.3)	0.49
Anticoagulation	24 (27.9)	21 (30.4)	0.73
Disease severity			
Severe pneumonia	56 (64.4)	55 (78.6)	0.05
Septic shock vasopressor	3 (3.5)	2 (2.9)	1.00
Aggressive fluid resuscitation	2 (2.3)	0 (0.0)	0.50
Clinical variables before CPAP treatment			
Confusion	7 (8.1)	2 (2.9)	0.30
Temperature C (n=153)	37.3±1.1	37.6±0.9	0.12
Systolic blood pressure mmHg (n=156)	130 (115–140)	130 (120–140)	0.87
Diastolic blood pressure mmHg (n=156)	75 (70–85)	80 (70–85)	0.69
Heart rate bpm (n=156)	88.3±15.6	86.5±14.5	0.47
Respiratory rate breaths·min^{-1} (n=153)	28 (24–32)	25.5 (21–30)	0.09
Respiratory rate ⩾30 breaths·min^{-1}	37 (43.5)	20 (29.4)	0.07
S_{pO_2}% (n=154)	93 (89–97)	95.5 (90–97)	0.41
Blood gas analysis before CPAP treatment			
pH (n=155)	7.48 (7.45–7.51)	7.47 (7.45–7.50)	0.91
P_{aCO_2} mmHg (n=157)	33.0±5.0	32.9±5.9	0.89
P_{aO_2} mmHg (n=157)	65 (53–83)	75.5 (60–96)	0.009
P_{aO_2}:F_{IO_2} ratio (n=157)	136 (95.0–204.8)	152 (100–202)	0.85
P_{aO_2}:F_{IO_2} ratio classes			
P_{aO_2}:F_{IO_2} ratio ⩽100 mmHg	23 (26.4)	18 (25.7)	0.90
100 mmHg <P_{aO_2}:F_{IO_2} ratio ⩽200 mmHg	39 (44.8)	34 (48.6)	
200 mmHg <P_{aO_2}:F_{IO_2} ratio ⩽300 mmHg	25 (28.7)	18 (25.7)	
Blood tests before CPAP treatment			
White blood cells cell·mm^{-3} (n=156)	7060 (5550–9630)	8000 (5490–10 450	0.45
Platelets cell·mm^{-3} (n=155)	227 00 (169 000–336 000)	199 000 (142 000–264 500)	0.02

Continued

TABLE 1 Continued

	CPAP success	CPAP failure	p-value
D-dimer μg·L^{-1} (n=126)	793 (561.0–1242.5)	1098 (667–2444)	0.03
Ferritin μg·L^{-1} (n=123)	1484 (832–2732)	1558.5 (1049–2830)	0.54
IL-6 ng·L^{-1} (n=125)	46.6 (19–75)	134 (77.9–266)	<0.0001
C-reactive protein, mg·dL^{-1} (n=157)	13.6 (8.4–44.0)	15.6 (10.8–25.8)	0.49
CPAP initiation and treatment			
F_{IO_2} % (n=154)	50 (50–60)	60 (50–70)	<0.0001
PEEP cmH_2O (n=154)	10.4±2.2	11.4±2.4	0.01
Increase of P_{aO_2}:F_{IO_2} ratio of at least 20% from oxygen therapy to CPAP	53 (64.6)	33 (48.5)	0.047
Increase of P_{aO_2}:F_{IO_2} ratio of at least 30% from oxygen therapy to CPAP	51 (62.2)	27 (39.7)	0.006
Days of CPAP treatment (n=153)	8 (5–14)	4 (3–7)	<0.0001
CPAP complications			
Pneumothorax	0 (0.0)	1 (1.4)	0.45
Pneumomediastinum	0 (0.0)	2 (2.9)	0.20
Haemodynamic instability	0 (0.0)	9 (12.9)	0.001
Intolerance[#]	10 (11.5)	11 (15.7)	0.44
Ulcer	2 (2.3)	0 (0.0)	0.50
Study outcomes			
Weaning from CPAP to oxygen therapy	84 (96.6)	6 (8.6)	<0.0001
Days from CPAP initiation to weaning to oxygen therapy (n=87)	7 (4–12)	7 (1–8)	0.31
Intubation	0 (0.0)	34 (48.6)	<0.0001
Days from CPAP initiation to intubation (n=34)		3 (2–5)	
Mortality in HDU	0 (0.0)	36 (51.4)	<0.0001
Days from CPAP initiation to HDU mortality (n=36)		5 (3–10)	
Length of hospitalisation (n=138)	18 (14–25.5)	8 (4–22)	<0.0001
In-hospital mortality	0 (0.0)	45 (64.3)	<0.0001
Days from CPAP initiation to in-hospital mortality (n=45)	0 (0–0)	6 (4–11)	

Data are presented as n (%), median (interquartile range), mean±SD, unless otherwise stated. BMI: body mass index; bpm: beats per minute; S_{pO_2}: oxygen saturation measured by pulse oximetry; P_{aCO_2}: arterial carbon dioxide tension; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; IL: interleukin; PEEP: positive end-expiratory pressure; HDU: high dependency unit. [#]: among them, four patients discontinued helmet CPAP.

The present study has several limitations which can limit the generalisability of our results. Among those, the lack of a control group and different standard operating procedures across the three centres, as well as the lack of important information, including the daily length of CPAP treatment, might reduce the inference. However, this is the first experience which evaluated outcomes in COVID-19 patients undergoing helmet CPAP in a multicentre, prospective study. In conclusion, the application of helmet CPAP in COVID-19 patients should be carefully considered and monitored to prevent a delayed endotracheal intubation.

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