Evaluation of $PaCO_2$ trend in COVID-19 patients undergoing helmet CPAP in the emergency department

Nicolò Capsoni,[1] Daniele Privitera,[1] Chiara Airoldi,[2] Silvia Gheda,[1] Annamaria Mazzone,[1] Gianluca Terranova,[1] Filippo Galbiati,[1] Andrea Bellone[1]

[1]Department of Emergency Medicine, ASST Grande Ospedale Metropolitano Niguarda, Milan;
[2]Department of Translation Medicine, University of Piemonte Orientale, Novara, Italy

Abstract

The use of continuous positive airway pressure (CPAP) in COVID-19 hypoxemic respiratory failure (h-ARF) under a strict protocol has been described to be highly efficient. However, early prediction of failure is crucial to avoid delayed intubation. Lower $PaCO_2$ values may represent a higher inspiratory effort and, therefore, may help identify patients at greatest risk of CPAP failure. Aim of this study was to observe the $PaCO_2$ trend of COVID-19 patients with h-ARF before and after the initial treatment with helmet-CPAP. A case series study was conducted from November 2020 to March 2021. All adult patients with h-ARF secondary to COVID-19 treated with helmet-CPAP and eligible for endotracheal intubation were observed. Of a total of 54 patients, 32 (59.3%) underwent intubation. Seven (12.9%) patients died in the ETI group, and none in the non-ETI group. Median PaO_2/FiO_2 ratio on admission was 91mmHg [IQR 68-185] *vs.* 104mmHg [IQR 85-215] (p=0.137) in the ETI e non-ETI group, respectively. No differences were found either for $PaCO_2$ values on admission (31.5mmHg [IQR 27-35] *vs.* 29.3mmHg [IQR 27.7-40]) and for $PaCO_2$ variations after 120 minutes of CPAP (+2.38 mmHg ± 3.65 *vs.* +2.73 mmHg ± 3.96). Changes in $PaCO_2$ values were observed during an initial helmet-CPAP trial, but no differences were found in those undergoing endotracheal intubation as compared to the others.

Correspondence: Nicolò Capsoni, Department of Emergency Medicine, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy.
E-mail: nicolo.capsoni@gmail.com

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Introduction

The use of continuous positive airway pressure (CPAP) in COVID-19 respiratory failure under a strict protocol has been described to be highly efficient. However, early prediction of failure is crucial to avoid delayed intubation.[1–3] Even though risk factors have previously been proposed to predict CPAP failure, a leading role is played by a high respiratory drive, whose accurate measurement, especially its non-invasive evaluation, remains a challenge.[4–7] In the Emergency Department (ED), clinical evaluation with respiratory parameters and blood gases are the first useful tools helping healthcare professionals, nurses, and physicians, firstly to assess the degree of respiratory distress at arrival, and subsequently to monitor the response to CPAP treatment over time.[8,9]

COVID-19 patients with hARF often present with an increased respiratory drive and low arterial carbon dioxide tension ($PaCO_2$) values due to hypoxia, impaired respiratory mechanics, and inflammatory stimulus.

Recently, in a post hoc analysis of the HENIVOT trial, evaluating helmet noninvasive ventilation as compared with a high-flow nasal cannula, patients with a $PaCO_2$ < 35 mmHg had a greater benefit from helmet non-invasive ventilation in terms of endotracheal intubation (ETI) than patients with normal or higher $PaCO_2$ (^{3} 35 mmHg).[10] The authors postulated that lower $PaCO_2$ values might represent a higher inspiratory effort and therefore may help identify patients who are at the greatest risk for non-invasive treatment failure during spontaneous breathing.[10] Anyway, so far, no one has demonstrated that the $PaCO_2$ trend, in addition to other non-invasive respiratory parameters, may help evaluate the patient's response to CPAP.

The aim of this case series was to describe the $PaCO_2$ trend of COVID-19 patients undergoing a first helmet-CPAP (H-CPAP) treatment in the emergency department according to a local proto-

col. Other respiratory parameters, H-CPAP failure, defined as the need for ETI, and in-hospital mortality were also assessed.

Materials and Methods

This case series was conducted between 13th November 2020 and 3rd March 2021 in the Emergency Department of the ASST Niguarda Hospital, Milan, Italy. The study was approved by the local ethical committee of Milano Area 3 (approval number 338-18052022). Owing to retrospective and de-identified data collection, the need for informed consent was waived.

Patients admitted to the ED with ARF due to COVID-19 pneumonia treated with H-CPAP, according to our local protocol and eligible for ETI, were included in the study.[11] Diagnosis of COVID-19 pneumonia was made if typical computed tomography scan patterns were present (ground-glass opacities, crazy-paving pattern, consolidations) and a SARS-CoV2 infection was confirmed by positive real-time reverse transcriptase-polymerase chain reaction assay of the nasopharyngeal swab.[12]

Inclusion criteria were age 18 years or older, preserved state of consciousness defined as Kelly ≤ 3, stable hemodynamics, SpO_2 level < 94% and respiratory rate (RR) ≥ 28 despite oxygen therapy supplied for at least 15 minutes through a face mask, according to our local protocol.

Exclusion criteria were the need for immediate intubation, altered state of consciousness, hemodynamic instability defined as systolic pressure <90 mmHg unresponsive to fluids replacement or requiring amines and/or major arrhythmias, inability to protect the airways, recent surgery on the skull or esophagus, trauma and craniofacial burns, and undrained pneumothorax. Patients who received a Do Not Intubate (DNI) order due to extremely poor functional status prior to admission, very low predicted probability of hospital survival and comorbidities, were also excluded.

The ETI eligibility and the decision to intubate the patient was based on a multidisciplinary discussion between the emergency physician in charge and the critical care physician, after discussion with the senior ICU physician when necessary. Clinical criteria were mainly used for ETI: respiratory arrest, respiratory pauses with loss of consciousness, severe hemodynamic instability, septic shock, multi-organ failure, need for sedation, worsening of vigilance (an increase of the Kelly scale >3), persistence or worsening of respiratory distress (presence of use of accessory respiratory muscles or paradoxical abdominal movement), PaO_2/FiO_2 value reduction and muscular exhaustion despite CPAP/non-invasive ventilation treatment.

CPAP local protocol

All the enrolled patients started a 120 minutes trial H-CPAP, following a local protocol, with a strict nursing evaluation and monitoring. CPAP was delivered through the helmet and high-flow-generating devices, able to deliver a minimum of 60 L/min flow required to match the patient's inspiratory flow and avoid CO_2 rebreathing.[13] Air-oxygen blenders ("BLENDER"; RM/145-2, Flow-Meter S.p.A., Levate, Italy), turbine (Monnal T75, Air Liquide Medical Systems, Paris, France), and three Venturi systems (EasyFlow, Dimar, Mirandola, Italy; 9293/D, Harol, S. Donato Milanese, Italy; Whisperflow, Philips Respironics, Murrysville, PA, USA) were used, according to the availability of the moment.[14]

The initial settings were a PEEP of 7.5 cm/H_20, a Flow ≥ 60L/min and a FiO_2 titrated to reach a SpO_2 ≥ 94% and a RR ≤ 25 bpm. PEEP was increased by 2.5 cm/H_2O up to a maximum of 12,5 cm/H_2O every 30 minutes in case of failure to reach the RR target. To limit air contamination, HME or electrostatic filters were applied at the expiratory port of the helmet-CPAP, and because of PEEP increase inside the helmet due to the filter application, PEEP was monitored with a manometer every different step up.[15,16] To increase patient comfort, counterweights instead of shoulder straps and earplugs were used, and nurses focused their attention on the interventions that contribute to increasing the patient's comfort to maximize the acceptability of the interface.[17]

Data collection

Vital signs and ventilation parameters were prospectively recorded before the CPAP trial was started and then every 30 minutes until the end of the trial. SpO_2, RR, PEEP, FiO_2 and body temperature were recorded before the CPAP trial was started and then every 30 min until the end of the trial (t0 - t30 e t60 e t90 e t120). Arterial blood gases were recorded before and after 120 minutes of CPAP. Demographics, comorbidities, and clinical findings at admission were recorded. Patients were followed until hospital discharge.

Data analysis

Sociodemographic variables and clinical data were reported as absolute and relative frequencies for categorical variables, while for numerical ones, the mean, and the corresponding standard deviation (SD) or median and interquartile range (IQR) were reported as appropriate. To explore the association between ETI and sociodemographic and clinical variables X^2 test or Fisher's exact test, and the student or Mann-Whitney U test were used.

Then, parameters related to the use of CPAP (FiO_2, PEEP, RR, and SpO_2) were evaluated in time using a mixed model for repeated measures to compared ETI and non-ETI group. Particularly, each parameter was considered as outcome and time was included as covariate; Beta and 95% confidence intervals [95% CI] were reported. A graphical representation was also reported to better visualize the time trend in each group. The significant threshold was set to 0.05 (two-tailed and all statistical analyses were performed using the SAS software (version 9.4).

Results

A total of 54 patients were observed. Forty-six (85.2%) were males, and the mean age was 62 years. Comorbidities and clinical findings are reported in Table 1. The median PaO_2/FiO_2 was 100 mmHg [72.5-192.5], and the median $PaCO_2$ was 32.9 [29-35] mmHg.

Twenty-two patients (40.7%) underwent ETI after the first trial of H-CPAP. There was no difference in PaO_2/FiO_2 ratio values between ETI and non-ETI groups (91 mmHg [IQR 68-185] *vs.* 104 mmHg [IQR 85-215], p=0.137, respectively). No differences were found either for $PaCO_2$ values on admission (31.5mmHg [IQR 27-35] *vs* 29.3mmHg [IQR 27.7-40], p=0.399, respectively) and for $PaCO_2$ variations after the CPAP trial (mean 2.38mmHg ±3.65 *vs* 2.73 mmHg ±3.96, p=0.556, respectively). ETI was performed after 1 [0-4] day of CPAP.

Respiratory and CPAP-related parameters (PEEP, FiO_2, RR, and SpO_2) and their variation over time are shown in Figure 1, while in supplementary material we reported the value of parameters in time.

Considering the models with CPAP-related parameters and ETI as a covariate, statistically significant changes between the

two groups were found for PEEP (p=0.03) and SpO_2 (p=0.046). Particularly, the ETI groups than non-ETI had a higher value of PEEP of 0.58 [95% CI 0.05; 1.11] and lower value of SpO_2 of -1.00 [-1.98; -0.01]. No significant changes were found for FiO_2 (p=0.084) and RR (p=0.102). Of 54 patients, 7 (12.9%) died, all of them after ETI, whereas 39 (72.2%) were discharged, and 8 ETI patients (14.8%) were lost during follow-up because they transferred to other hospitals. The median length of hospital stay was for ETI and not ETI patients 33 [18-47] *vs* 16 [8-23] days - p=0.0032, respectively.

Discussion

As known, non-invasive ventilation failure is an independent risk factor for death in patients with hARF.[18,19] Although burdened by the risk of treatment failure, in real-life experience, a first short CPAP trial was often attempted in the ED in patients with hARF due to COVID-19 to ameliorate hypoxia and dyspnea while proceeding with the first diagnostic tests and while evaluating ETI eligibility and need.[1,2] A careful selection of patients and strict bedside monitoring are mandatory during the first hours of CPAP trial to assess the response in terms of gas exchange and respiratory distress. Different CPAP protocols previously proposed a progressive upgrade of oxygen and respiratory support with a strict clinical patients monitor.[1,2] Clinical evaluation of respiratory distress and mechanics, respiratory parameters, and blood gases are often the only non-invasive bedside instruments available to ED clinicians and nurses to roughly quantify the degree of respiratory failure and inspiratory effort during CPAP treatment. As postulated by Grieco *et al.*,[10] lower $PaCO_2$ values may represent a higher inspiratory effort. Therefore, in our study, we evaluated $PaCO_2$ values and trends as potential simple bedside surrogates of increased respiratory drive in COVID-19 patients during CPAP treatment. Most of our patients had severe respiratory failure (PaO_2/FiO_2 ratio 100 mmHg [72.5-192.5]) with significant hypocapnia ($PaCO_2$ 32,9 mmHg [29-35]). We observe a general increase in $PaCO_2$ after 120 minutes of the CPAP trial, with a reduction of RR and an increase of SpO_2, with no significant difference in those undergoing ETI compared to the others. Statistically significant changes between the two groups were found for PEEP and SpO_2. According to our protocol, higher values of PEEP were applicated to patients with persistent respiratory distress and higher RR, thus suffering a more severe respiratory failure. Therefore, the higher PEEP and lower SpO_2 values probably reflected a higher severity of the disease.

The generalizability of our results is undoubtedly limited by the retrospective study design and the small sample size. Furthermore, we evaluated the $PaCO_2$ trend after 120 minutes, given that a longer CPAP trial in hARF could have delayed ETI

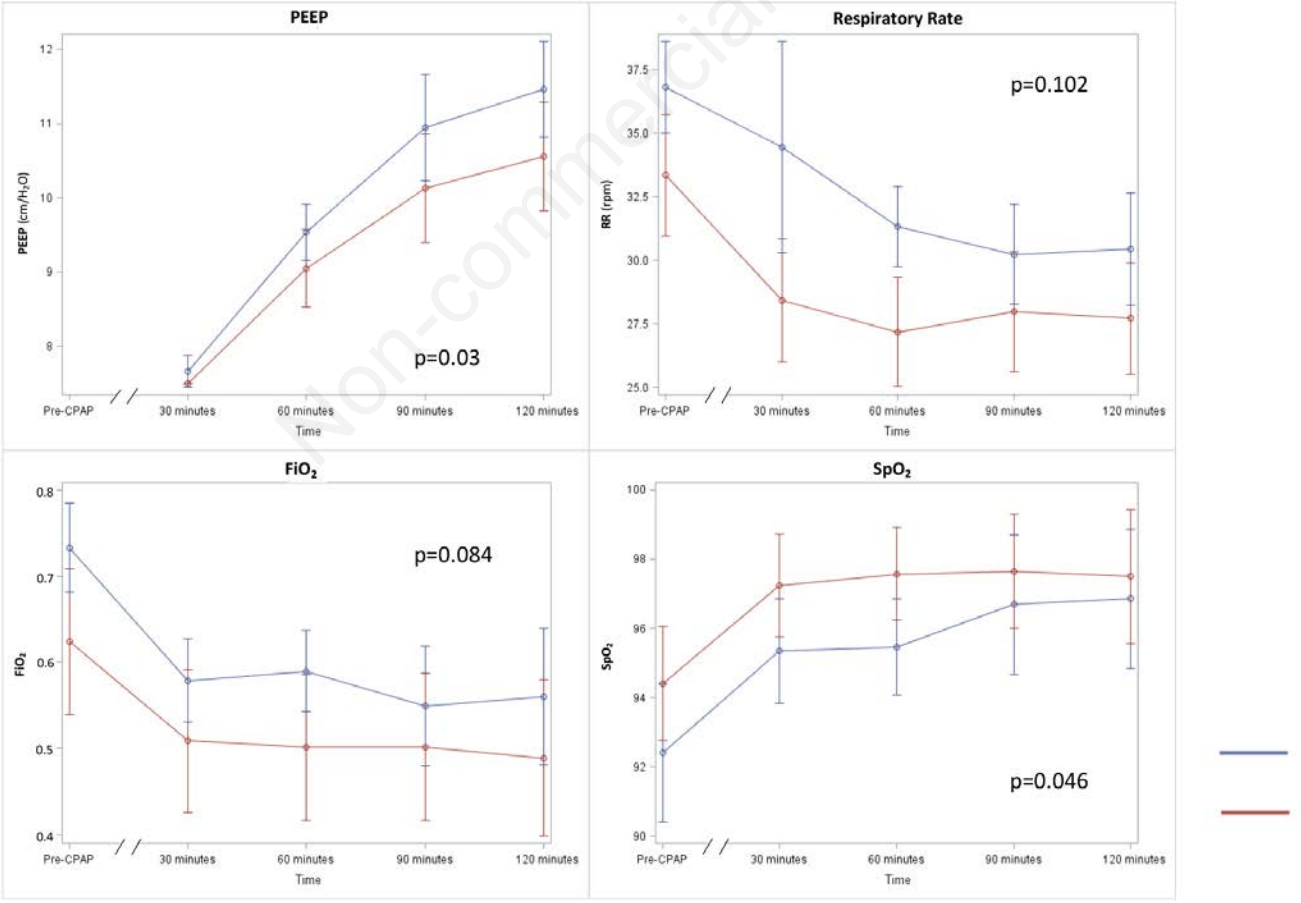

Figure 1. PEEP, Respiratory Rate, SpO_2, and FiO_2 values over time in the ETI group (blue line) and non-ETI group (red line). PEEP, positive end-expiratory pressure; RR, respiratory rate; FiO_2, fraction of inspired oxygen; SpO_2, peripheral oxygen saturation.

Table 1. Baseline characteristics, clinical findings, blood gas analysis and outcomes of the study population and of the ETI and non-ETI group.

	All (n=54)	ETI (n=22)	Non-ETI (n=32)
Females	8 (14.81)	2 (9.09)	6 (18.75)
Age, mean (±SD)	62.24 (±9.88)	57.18 (±10.06)	65.72 (±8.23)
Comorbidities			
Obesity, n (%)	12 (22.22)	3 (13.64)	9 (28.13)
Hypertension, n (%)	28 (51.85)	11 (50.00)	17 (53.13)
Diabetes, n (%)	6 (11.11)	1 (4.55)	5 (15.63)
Immunosuppression, n (%)	4 (7.41)	1 (4.55)	3 (9.38)
Active cancer, n (%)	2 (3.70)	1 (4.55)	1 (3.13)
Pulmonary disease, n (%)	4 (7.41)	3 (13.64)	1 (3.13)
Heart disease, n (%)	8 (14.81)	3 (13.64)	5 (15.63)
Chronic renal failure, n (%)	3 (5.56)	0	3 (9.38)
Autoimmune disease, n (%)	1 (1.85)	0	1 (3.13)
Symptoms			
Fever, n (%)	39 (72.22)	17 (77.27)	22 (68.75)
Cough, n (%)	19 (35.19)	9 (40.91)	10 (31.25)
Dyspnea, n (%)	47 (87.04)	20 (90.91)	27 (84.38)
Asthenia and/or myalgia, n (%)	14 (25.93)	10 (45.45)	4 (12.50)
Dysgeusia and/or anosmia, n (%)	2 (3.70)	2 (9.09)	0
Days from symptoms onset to hospital admission, median [IQR]	2 [2-3]	3 [2-3]	2 [1-3]
Blood gas analysis before CPAP trial			
pH	7,47 [7,44-7,49]	7,48 [7,45-7,49]	7,46 [7,44-7,50]
$PaCO_2$, mmHg	32,9 [29-35]	31,5 [27-34,9]	29.3 [27,7-34]
PaO_2/FiO_2 ratio, mmHg	100 [72,5-192,5]	91 [68-185]	104 [85-215]
$PaCO_2$ variations after 120 minutes of CPAP treatment, mean (±SD)		+2,38 mmHg (±3,65)	+2,73 mmHg (±3,96)
Outcomes			
In-hospital mortality, n (%)	7 (12,9%)	7 (50%)	0
Days of length of stay, median [IQR]	23 [12-33]	33 [18-47]	16 [8-23]
Days of NIV, median [IQR]	5 [1-9]	1 [0-4]	7 [4-12]

N, number; FiO_2: fraction of inspired oxygen; SpO_2, peripheral oxygen saturation; CPAP, continuous positive airway pressure; NIV, non-invasive ventilation.

and have been harmful. It could be reasonable to evaluate a $PaCO_2$ improvement after a longer time-lapse. Moreover, other $PaCO_2$ determinants besides the hypoxemic stimulus correction should be considered. However, based on our knowledge, this is the first study in which the $PaCO_2$ trend was evaluated after 120 minutes of a standardized CPAP trial. Non-invasive repeatable and easy-to-implement monitoring methods to assess the inspiratory effort and evaluate the risk of CPAP failure are needed to guide clinicians. Among these diaphragmatic ultrasound, allowing the evaluation of diaphragmatic mass and thickening fraction, represents an interesting new bedside tool.[20,21]

The hypothesis that a lower $PaCO_2$ may represent a higher inspiratory effort and that its trend may help to evaluate CPAP response is interesting and need well-sized observational studies to be evaluated.

Conclusions

Changes in $PaCO_2$ values were observed during the first closed-monitored CPAP trial, but no difference was found in those undergoing ETI compared to others. Larger studies are necessary to confirm our results, evaluate the efficacy of non-invasive surrogate parameters to assess the inspiratory effort and guide clinicians and nurses treating hARF with CPAP.

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