EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Research letter

Continuous positive airway pressure to avoid intubation in SARS-CoV-2 pneumonia: a two-period retrospective case-control study

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Please cite this article as: Oranger M, Gonzalez-Bermejo Jésus, Dacosta-Noble P, *et al*. Continuous positive airway pressure to avoid intubation in SARS-CoV-2 pneumonia: a two-period retrospective case-control study. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.01692-2020).

Title

Continuous positive airway pressure to avoid intubation in SARS-CoV-2 pneumonia: a two-period retrospective case-control study.

Subtitle

CPAP in COVID19 pneumonia

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Introduction

SARS-CoV-2 can cause severe pneumonia requiring invasive mechanical ventilation [2], in the context of atypical acute respiratory distress syndrome (ARDS)[3]. The magnitude of the epidemic places an unprecedented pressure on intensive care units (ICU), making avoidance of intubation a critical issue.

Supplemental oxygen is the first-line treatment of ARDS. When escalation is needed, pre-intubation approaches carry the risk of delaying intubation and increasing mortality[4]. Noninvasive ventilation (NIV) is not recommended [5] but high-flow nasal oxygen (HFNO) may decrease the need for intubation without impacting mortality [5, 6] Mostly because of an early negative report [7], continuous positive airway pressure (CPAP) remains largely undocumented in ARDS. In SARS-CoV-2 pneumonia, evidence-based guidelines are lacking[8] but CPAP could prove useful [9].

In this context, on March 20,2020, the French learned society for respiratory medicine circulated a clinical management algorithm derived from the Italian experience and suggesting the use of CPAP in SARS-CoV-2 patients requiring oxygen escalation [9]. This algorithm was implemented in our department on March 24, 2020, in a context of limited HFNO availability and environmental contamination concers.

We designed this retrospective study to evaluate the impact of the CPAP strategy on intubation rate. We compared the period immediately before the algorithm implementation (March 11-March 23, 2020) with the period immediately after (March 24-April 8), testing the hypothesis that CPAP can avoid intubation in patients with severe forms of SARS-CoV-2 pneumonia over the first week of their management.

Patients and Methods

This observational study with short-term historical controls was conducted in the 25-bed pulmonology unit of a 1600-bed university hospital (Pitié-Salpêtrière, Paris, France). It was approved the institutional review board of the French learned Society for respiratory medicine (CEPRO2020-024). Patients were informed of the use of their anonymized data and given the opportunity to refuse it.

According to an *ad hoc* hospital policy, all the patients admitted to the pulmonology unit between March 11 and April 8, 2020) had to have laboratory-confirmed SARS-CoV-2 infection and acute respiratory distress (respiratory rate ≥25, bilateral pulmonary infiltrates on chest X-ray or CTscan, need for standard oxygen between 3 and 6 $L.min^{-1}$ to maintain SpO2 ≥ 92%). Among them, those requiring escalating oxygen therapy ≥ 6 $L.min^{-1}$ to

maintain SpO_2 ≥ 92% were included (Figure 1). Two consecutive periods were compared (#1: March 11-23, controls; #2: March 24-April 8, cases). During period #1, escalation consisted only in increasing supplemental oxygen, up to 15 $L.min^{-1}$. During period #2, CPAP was delivered on an as needed basis, with a minimum of 2 hours twice a day and continuous nocturnal administration. CPAP was administered using a face mask connected a home mechanical ventilator in most cases, or to a Boussignac positive pressure valve. CPAP was initially set at 10cmH_2O and then adjusted between 8 and 12 cmH_2O according to clinical tolerance, leaks and SpO_2. The expiratory limb of the circuit was equipped with an antimicrobial filter. Patients were not included in the presence of alveolar hypoventilation ($PaCO_2$ ≥ 45 mmHg), if they received CPAP during period #1, or when they had to be intubated during the first 30 minutes of CPAP during period #2.

The outcome was intubation at day 7, or death in the patients with a "do not intubate" (DNI) decision (collegial discussion between pulmonology and ICU staff, on admission or at any timethereafter, mainly taking into account the patient's own opinion when reliable, age, frailty score and comorbidities). Criteria for intubation were haemodynamic instability, neurologic deterioration, worsening respiratory failure with respiratory rate above 40 breaths and high respiratory-muscle recruitment, acidosis with a pH below 7.35, SpO2 below 90% for more than 5 minutes without response to pre-intubation approaches.

Clinical and laboratory data were obtained from electronic medical records. Missing data were not imputed. The statistical analysis was performed using Prism v6® (Graphpad, USA). Continuous variables are summarized as medians and interquartile ranges and comparted using the Mann-Whitney U-test. Categorical variables are summarized as numbers and compared using Fisher's exact test. Intubation-free survival curves were compared by log-rank test. Differences were considered significant for $p< 0.05$.

Results

Over the whole period of interest, 97 patients COVID patients with acute respiratory failure criteria were admitted 66 patients were eligible for inclusion, and 52 were included (14 controls and 38 cases) (Figure 1). There was no significant difference between controls and cases regarding age (62 [54-72] vs. 63 [55-70]), gender (13 men vs 26), body mass index (26.7 [23.0-33.0] $kg.m^{-2}$ vs. 27.6 [24.2-34.4]), tobacco smoking (3 vs. 9), respiratory and cardiovascular comorbities, clinical data upon admission (body temperature, heart rate and arterial pression), biological data (white cell count, lymphocyte count, C-reactive protein, procalcitonin, D-dimers) or radiological data (bilateral infiltrates in 100% of cases). Physiological severity on admission was not different (Simplified acute physiology score II 24 [21-28] vs. 27 [22-30]) and respiratory severity was comparable (respiratory rate 30 [20-35]

vs. 27 [23-32]; use of accessory muscles 100%; PaO2 under oxygen 69.0 [61.0-83.0] mmHg vs. 71 [63.5-88.5], PaCO2 32.0 [28.0-38.0] mmHg vs. 30.5 [30.5-37], pH 7.48 [7.46-7.51] vs. 7.48 [7.46-7.51]; oxygen needed to maintain SpO2 ≥92% 3 [2-6] vs. 5 [3-6]). There was also no difference during the two periods between treatment received by controls and cases (hydroxychloroguine 8 vs 20; antiviral drugs 0 vs. 1; tocilizumab 0 vs1; corticosteroids 0 vs. 1) and between the number of inclusions in randomized trials (0 vs. 6)

Cases received CPAP for 5 [2-7.5] days with a daily use of 8 [4-11] hours.

Six intubations and two deaths without intubation were recorded at day 7 during period #1 (57%), vs. 9 intubations and no deaths during period #2 (23%)($p = 0.043$). Among DNI patients there were 2 deaths in 2 patients during period #1, vs. no death in 6 patients during period #2 ($p = 0.036$). 7-day intubation-free survival rate was significantly better during period #2 ($p = 0.021$, Figure 1). Median time to intubation or death was 5.5 days during period #1 and was not reached at day 7 during period#2. Identical results were observed at day 14.

Discussion

Our findings indicate that CPAP is feasible in deteriorating COVID-19 patients managed in a pulmonology unit. They suggest that CPAP can avoid intubation at 7 days and at 14 days, particularly in patients with a previous DNI decision, which resembles similar observations with NIV in patients having declined intubation[10].

This result must be interpreted very cautiously due to the monocentric retrospective and non-randomized nature of the study, its small size and a smaller number of controls than cases. Yet several elements compensate for these weaknesses. The two periods were short and consecutive, limiting the risk of practice variations. Identical treatment protocols and personnel-to-patient ratio were used; intubation criteria were unchanged and there was no shortage of ICU beds. Patients treated during period #1 did not significantly differ from patients treated during period #2. Because we generally used high-end home mechanical ventilators to apply CPAP (due to immediate availability), we could ascertain the quality and duration of treatment. Of note, simpler devices have been used to apply CPAP [9] including in our patients, and even if potential “technical” differences may be found between methods, there is no reason to think they should provide different results.

Regarding safety, none of our patients receiving CPAP had to be intubated under high emergency or cardiac arrest conditions. We acknowledge that may unduly delay intubation in non-expert hands, and insist on the notion that intubation should not be delayed

in the absence of a rapid and clear response to treatment. The proportion of caregivers contaminated by SARS-CoV-2 was similar during period #2 (6%)and during period #1 (10%).

Our observations need to be corroborated and can only justify prospective randomized trials. If confirmed, they would be of particular interest in the context of mass critical care or healthcare systems in low income countries.

Acknowledgements and conflict of interest disclosures

1) the authors gratefully acknowledge the help of the following persons, listed as collaborators of the study :

ARNULF Isabelle, ATTALI Valérie, BELHACHIMI Zakaria, BEURTON Alexandra, BOUZNAD Yasmine, DELEMAZURE Julie, DELERIS Robin, DODET Pauline, DRES Martin, DUGUET Alexandre, EL-KOUARI Fadwa, ESTEBAN-AMARILLA Christina, GALARZA JIMENEZ Maria Alejandra, GAZANIOL Claire, HAUDEBOURG Luc, HAZIOT Noémie, HELLY DE TAURIERS Pierre, LAVENEZIANA Pierantonio, LECRONIER Marie, LEMAREC Julien, LONDNER Cécile, MAISONOBE Jeanne, MALRIN Roxane, MAYAUX Julien, MENDOZA Alexis, MORA Pierre, MORAWIEC Elise, MOURTADA Leila, NEMLAGHI Safaa, OHAYON Raphaelle, ORCEL Brigitte, REDOLFI Stefania, RIQUIER Claire, SOYEZ Bérénice, STRAUS Christian, VIROLLE Sara, WOZNIAK Estelle.

2) The authors have no conflict of interest to declare regarding this study.

References

1. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020.
2. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS, China Medical Treatment Expert Group for C. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020.
3. 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.
4. Demoule A, Girou E, Richard JC, Taille S, Brochard L. Benefits and risks of success or failure of noninvasive ventilation. *Intensive Care Med* 2006: 32: 1756-1765.
5. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, Navalesi PMOTSC, Antonelli M, Brozek J, Conti G, Ferrer M, Guntupalli K, Jaber S, Keenan S, Mancebo J, Mehta S, Raoof SMOTTF. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J* 2017: 50.
6. Wang K, Zhao W, Li J, Shu W, Duan J. The experience of high-flow nasal cannula in hospitalized patients with 2019 novel coronavirus-infected pneumonia in two hospitals of Chongqing, China. *Ann Intensive Care* 2020: 10: 37.
7. Delclaux C, L'Her E, Alberti C, Mancebo J, Abroug F, Conti G, Guerin C, Schortgen F, Lefort Y, Antonelli M, Lepage E, Lemaire F, Brochard L. Treatment of acute hypoxemic nonhypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask: A randomized controlled trial. *JAMA* 2000: 284: 2352-2360.
8. Namendys-Silva SA. Respiratory support for patients with COVID-19 infection. *Lancet Respir Med* 2020: 8: e18.
9. Italian Thoracic Society (AIPO – ITS), Italian Respirarory Society (SIP/IRS). Managing the Respiratory care of patients with COVID-19 - English version. *available at http://wwwaiponetit/news/speciale-covid-19/2426-managing-the-respiratory-care-of-patients-with-covid-19-english-versionhtml* 2020.
10. Azoulay E, Kouatchet A, Jaber S, Lambert J, Meziani F, Schmidt M, Schnell D, Mortaza S, Conseil M, Tchenio X, Herbecq P, Andrivet P, Guerot E, Lafabrie A, Perbet S, Camous L, Janssen-Langenstein R, Collet F, Messika J, Legriel S, Fabre X, Guisset O, Touati S, Kilani S, Alves M, Mercat A, Similowski T, Papazian L, Meert AP, Chevret S,

Schlemmer B, Brochard L, Demoule A. Noninvasive mechanical ventilation in patients having declined tracheal intubation. *Intensive Care Med* 2013: 39: 292-301.

Figure legend

Figure 1. Panel A : study flow chart. Panel B : Seven-day intubation-free survival.

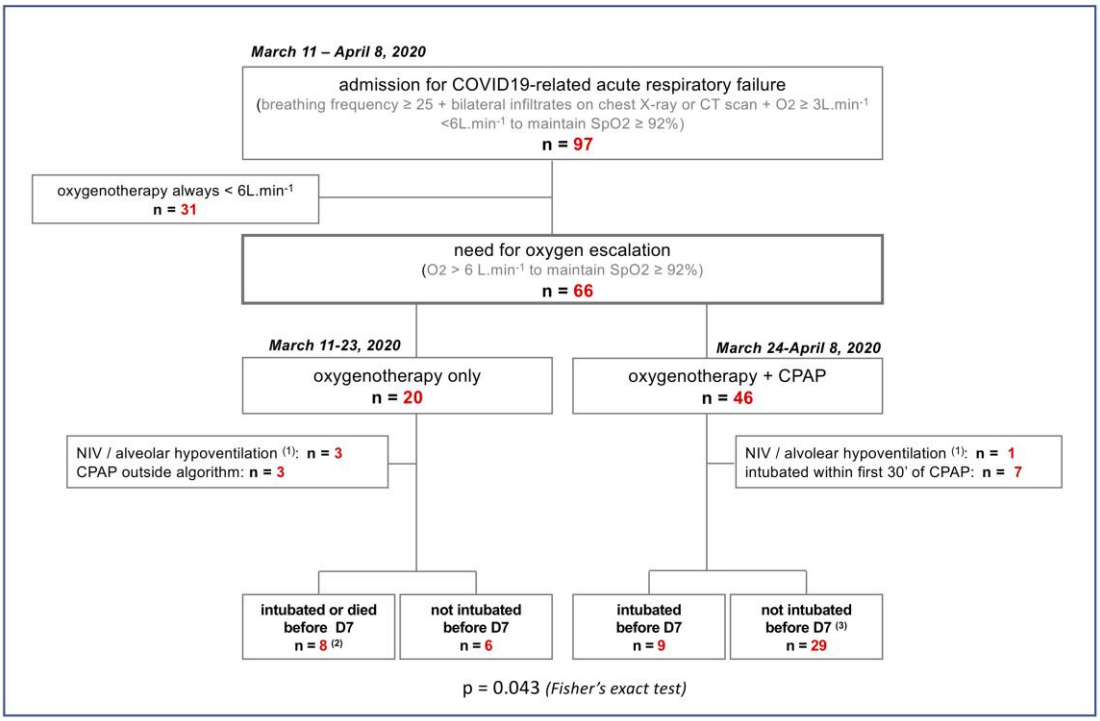
1. PCR COVID + and breathing frequency ≥ 25 and chest X-ray or CT scan abnormalities and need for ≥ 3L.min^{-1} <6L.min^{-1} to maintain SpO2 ≥ 92%

2. NIV, noninvasive ventilation; alveolar hypoventilation: PaCO2≥45 mmHg

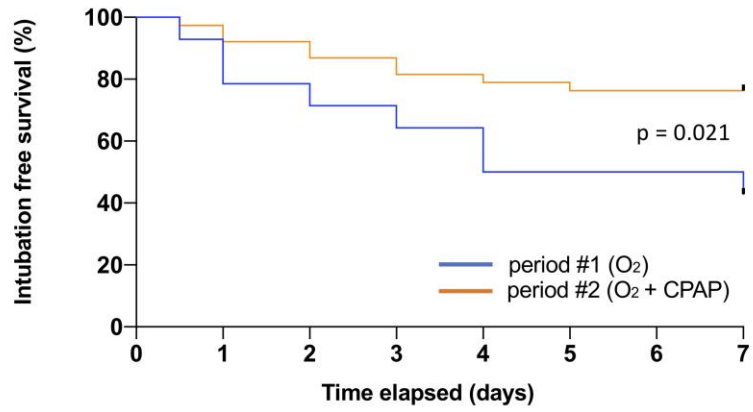
3.5 intubations and 3 deaths; 2 of of the deaths occurred in the 2 « do not intubate » patients

4. there were 6 patients with « do not intubate » decisions, none of whom died (p = 0.036 vs controls, Fisher's exact test)

Panel A



Panel B



Number at risk

period #1	14	13	11	10	9	9	6	6
period #2	38	37	35	33	31	30	30	29