Positive role of continuous positive airway pressure for intensive care unit patients with severe hypoxaemic respiratory failure due to COVID-19 pneumonia: A single centre experience

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Abstract

Objectives: Continuous positive airway pressure (CPAP) may be a useful treatment strategy for patients with severe COVID-19 pneumonia but its effectiveness in preventing mechanical ventilation is unknown. We aimed to evaluate the outcomes of COVID-19 patients treated with CPAP and determine predictors of CPAP response.

Design: This was a retrospective observational cohort study.

Setting: The study took place in the intensive care unit (ICU) at Royal Papworth Hospital (RPH) in Cambridge, UK.

Patients: We included all consecutive patients with confirmed COVID-19 pneumonia who were transferred from neighbouring hospitals between 14th March and 6th May, 2020 for consideration of ventilatory support.

Intervention: We instituted the use of CPAP for all patients who arrived in RPH not intubated and were not making satisfactory progress on supplemental oxygen alone.

Measurements and main results: Of 33 self-ventilating patients included in this study, 22 (66.7%) were male and the mean age was 54 ± 13.23 patients received CPAP. They were more hypoxaemic than those treated with oxygen alone (PaO2/FiO2 ratio; 84.3 ± 19.0 vs 170.0 ± 46.0 mmHg, p = 0.001). There was a significant improvement in PaO2/FiO2 ratio 1–2 hours after CPAP initiation (167.4 ± 49.0 from 84.3 ± 19.0 mmHg, p = 0.001). 14 (61%) patients responded to CPAP and 9 required intubation. There was no difference between these two groups in terms of the severity of baseline hypoxaemia (PaO2/FiO2 ratio; 84.5 ± 16.0 vs 83.9 ± 23.0 mmHg, p = 0.94) but CPAP responders had significantly lower C-reactive protein (CRP) (176 ± 83 vs 274 ± 63 mg/L, p = 0.007), interleukin-6 (IL-6) (30 ± 47 vs 139 ± 148 pg/mL, p = 0.037), and D-dimer (321 ± 267 vs 941 ± 1990 ng/mL, p = 0.003). CT pulmonary angiogram was performed in 6 out of 9 intubated patients and demonstrated pulmonary emboli in 5 of them. All patients were discharged from ICU and there were no fatalities.

Conclusions: In this cohort, CPAP was an effective treatment modality to improve hypoxaemia and prevent invasive ventilation in a substantial proportion of patients with severe respiratory failure. Accepting the small sample size, we also found raised biomarkers of inflammation (CRP and IL-6) and coagulopathy (D-Dimer) to be more useful predictors of CPAP responsiveness than the severity of hypoxaemia, and could help to guide intubation decisions in this clinical setting.

Keywords

COVID-19, SARS-CoV-2, CPAP, NIPPV, continuous positive airway pressure, non-invasive positive pressure ventilation

Introduction

Approximately 10% to 15% of patients infected with COVID-19 develop severe hypoxaemic respiratory failure (HRF) requiring admission to an intensive care unit (ICU) and invasive mechanical ventilation (IMV).¹,² Alternatives to IMV for selected patients with HRF include non-invasive positive pressure therapies such as continuous positive airway pressure

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(CPAP) or bi-level positive airway pressure (NIV). Avoiding IMV aims to reduce morbidity associated with it, including ventilator-induced lung injury, ventilator-acquired pneumonia, and prolongation of ICU stay.\(^5\) However, the role of CPAP or NIV to treat such patients is uncertain. Concerns include potentially high failure rates, worse outcomes in subsequently intubated patients, and airborne transmission of the virus.\(^4\) Accordingly, initial recommendations for managing HRF during COVID-19 pandemic have varied with some centres advocating early intubation and limited use of CPAP/NIV, and others advocating more universal trials of CPAP/NIV before intubation.\(^5\)–\(^7\)

There are few published data on the effectiveness of CPAP in COVID-19 pneumonia. Its role in preventing IMV has not been reported. We have therefore assessed the outcomes of patients admitted to ICU with HRF due to COVID-19 and treated with CPAP, and investigated factors associated with CPAP success.

**Material and methods**

**Patients and setting**

This was a single centre, retrospective, observational cohort study conducted at the Royal Papworth Hospital, Cambridge, United Kingdom, a tertiary centre with a large ICU and one of the nationally-commissioned centres for extra-corporeal membrane oxygenation (ECMO). In addition to increasing its ECMO capacity to 20 patients, the hospital also provided a critical care surge capacity for neighbouring district general hospitals to mitigate against the impact of excessive demand. All patients were diagnosed with COVID-19 pneumonia according to the WHO interim guidelines\(^8\) and had been judged by the referring and accepting clinical teams to require and be suitable for ICU level of care. Whilst some had already required intubation in their referring hospital, the study population comprises all consecutive patients transferred to our unit between 14th March and 6th May, 2020 and self-ventilating on arrival. Throat swabs were obtained on admission to confirm COVID-19 infection.

**CPAP treatment**

All patients who required high concentration oxygen to maintain oxygen saturation $\geq 94\%$ and remained tachypnoeic or breathless, or had increasing oxygen requirements were offered CPAP prior to intubation. Clinical decision-making, such as starting CPAP and/or intubation were taken by the attending clinical team based on standard criteria, including changes in PaO$_2$/FiO$_2$ ratio, respiratory rate, work of breathing and the tolerance of CPAP. CPAP was delivered via a non-vented total face or full face mask. A viral-bacterial filter was placed over the exhalation port of the circuit to reduce viral droplet dispersal. All staff attending to patients were donned in appropriate personal protective equipment (PPE) for aerosol-generating procedures, as per Public Health England guidelines.\(^9\) For the majority of patients, CPAP was initially delivered using a ventilator with an air-oxygen blender ((Maquet Servo-I (Soma Technology Inc., Bloomfield, CT) or Respironics V60 (Philips Respironics Inc., Murrysville, PA)). Anticipating a potential shortage of ICU ventilators, we transitioned CPAP-responder patients to a simpler portable device ((NIPPY 3+ or NIPPY 4 in a CPAP mode (Breas Medical Ltd., Stratford-upon-Avon, United Kingdom) or CPAP DreamStation (Philips Respironics Inc., Murrysville, PA)). CPAP was started at 5 cmH$_2$O and titrated to 10 cmH$_2$O, though higher levels of CPAP of up to 15 cmH$_2$O were required for some patients. Oxygen was titrated to maintain saturations between 92% and 96%. Patients were encouraged to lie in a prone or semi-prone position as tolerated and monitored closely for changes in vital parameters, apparent work of breathing and oxygenation status. In addition, a dedicated CPAP Task Team was created to provide regular review, including troubleshooting, ensuring consistency in CPAP application, titration of pressure and subsequent weaning from CPAP.

**Study outcomes**

The primary outcome of this study was to determine the proportion of CPAP responders defined as patients who received CPAP and did not require IMV. We also aimed to determine factors associated with CPAP response and establish mortality in this cohort.

**Data collection**

The study was approved by the hospital’s Research and Development department as a service evaluation. Anonymised data were collected retrospectively from Electronic Patient Records. The following information were extracted: patient demographics, co-morbidities, duration of symptoms, oxygen requirements, PaO$_2$/FiO$_2$ ratio and respiratory rate (RR) before and 1–2 hours after commencing CPAP, laboratory markers on admission, imaging obtained, CPAP level and duration of treatment, intubation status, length of ICU and hospital stay, and mortality.

**Statistical analysis**

Continuous data are presented as mean $\pm$ SD or median $\pm$ IQR depending on the distribution. Categorical variables are reported as numbers and percentages. Normality was checked using Shapiro-
Wilk test and by assessment of skewness and its standard error. Comparisons of clinical characteristics between the groups were performed using the independent-samples T-test or, if the data were not normally or approximately normally distributed, and in case of categorical variables, using the Mann-Whitney U test. To examine differences in pre- and post-CPAP respiratory variables, paired T-test or Wilcoxon test were used as appropriate. The level of significance for each comparison was set at \( p < 0.05 \). All analyses were conducted using SPSS software version 22.0 (IBM SPSS, IL, USA).

**Results**

A total of 91 patients were transferred to our ICU on the COVID-19 pathway between 14th March and 6th May 2020. Of these, 33 had not undergone tracheal intubation. They were middle aged, mostly men and of white ethnic background. Obesity was the most common comorbidity affecting 42.4% of patients. Median \( \text{FiO}_2 \) requirement was 0.8 ± 0.3 on admission, with 91% of all patients requiring 0.6 \( \text{FiO}_2 \) or greater to maintain adequate oxygenation (Table 1). Twenty three patients were commenced on CPAP. They were severely hypoxaemic with significantly lower \( \text{PaO}_2/\text{FiO}_2 \) ratio and higher RR than patients who continued to be treated with supplemental oxygen alone (Table 2). CPAP therapy resulted in a rapid improvement in \( \text{PaO}_2/\text{FiO}_2 \) ratio. There was no apparent change in observed respiratory rate but blood gas measurements performed on CPAP showed a slight increase in \( \text{PaCO}_2 \) and normalisation of mild respiratory alkalosis which would suggest reduction of minute ventilation during CPAP therapy (Figure 1 and Table 3). CPAP was successful for 14 patients (61%). In those patients mean CPAP treatment duration was \( 5.9 ± 3.6 \) days and the median pressure was \( 10 ± 2 \text{cmH}_2\text{O} \). Of the 9 patients who required tracheal intubation, 5 were intubated within 6 hours of starting CPAP. The remaining 4 patients were intubated at day 2, day 4, day 9 and day 18. Based on the ventilatory parameters recorded post-intubation, patients did not appear to be difficult to ventilate (mean Tidal Volume: 540 ± 87 ml; mean Mean Airway Pressure: 14.6 ± 2.2 cmH\(_2\)O; mean Peak Pressure: 25.7 ± 4.3 cmH\(_2\)O; mean Pressure Support set: 15.1 ± 3.3 cmH\(_2\)O; mean Positive End-Expiratory Pressure set: 10 ± 3 cmH\(_2\)O; \( n = 9 \)). There were no significant differences between CPAP responders and non-responders with respect to age, severity of baseline hypoxaemia, blood gas measurements, tidal volume, and magnitude of \( \text{PaO}_2/\text{FiO}_2 \) improvement on CPAP. However, on review of admission blood tests, CPAP responders had significantly lower C-reactive protein (CRP), interleukin-6 (IL-6), and D-dimer compared to non-responders (Table 4). Of these biomarkers, CRP was measured repeatedly every morning for all patients. To examine a dynamic behaviour of inflammation in people who responded versus those who failed CPAP therapy, we compared CRP change between day 1 and day 3 of admission. CRP increased in 42.9% of CPAP responders and in 77.8% of CPAP non-responders but the difference in these proportions and in the mean change in CRP between the groups did not reach statistical significance (\( p = 0.197 \) and \( p = 0.13 \) respectively, also see Figure 1). Among patients who required intubation beyond the first day of CPAP therapy, most of the biomarkers remained high or continued raising at intubation with the exception of one patient who underwent emergency intubation and tracheostomy at day 18 due to an unexpected acute airway obstruction rather than gradual deterioration in respiratory parameters (see supplement 1 for trends in biomarkers among the four patients intubated after 24 hours of CPAP therapy). CT pulmonary angio-gram (CTPA) was performed in 6 patients who did not respond to CPAP. Segmental and subsegmental pulmonary emboli were found in 5 of them. One further patient who was intubated could not undergo CTPA due to morbid obesity and was empirically fully anticoagulated based on clinical suspicion of PE. Only one patient in the CPAP-responder group had a CTPA scan. This was negative for pulmonary embolism.

| Table 1. Characteristics of self-ventilating patients with coronavirus-19 pneumonia. |
|------------------------------------------|
| **Number (\%)**                          |
|------------------------------------------|
| Number of patients: 33 (100)             |
| Age, mean ± SD, years: 54 ± 13           |
| Gender                                   |
| Male: 22 (66.7)                           |
| Female: 11 (33.3)                         |
| Ethnicity                                |
| White: 28 (84.8)                          |
| Others: 5 (15.2)                          |
| Duration of symptoms, mean ± SD, days: 8.4 ± 3.2 |
| Body mass index, mean ± SD, kg/m\(^2\): 29.3 ± 10.3 |
| Comorbidities                            |
| Obesity: 14 (42.4)                        |
| Hypertension: 9 (27.3)                    |
| Asthma or COPD: 5 (15.2)                  |
| Hyperlipidemia: 4 (12.1)                  |
| Cardiac conditions\(^a\): 3 (9.1)         |
| Diabetes mellitus: 2 (6.1)                |
| Oxygen requirement on admission           |
| Face mask, \( \text{FiO}_2 \) 0.4: 3 (9.0) |
| Face mask, \( \text{FiO}_2 \) 0.6\(^b\): 6 (18.0) |
| Face mask, \( \text{FiO}_2 \) 0.8\(^b\): 9 (27.0) |
| Non-rebreather mask, \( \text{FiO}_2 \) 0.9: 15 (46.0) |

Abbreviations: COPD: chronic obstructive pulmonary disease; \( \text{FiO}_2 \): fraction of inspired oxygen; SD: standard deviation.

\(^a\)Including ischemic heart disease, atrial fibrillation, heart failure.

\(^b\)Humidified oxygen therapy.
There were no fatalities in the entire cohort of 33 patients and all were discharged from ICU on supplemental oxygen with the exception of one patient who was diagnosed with severe obstructive sleep apnoea and was established on long-term CPAP therapy. The median ICU stay for the 23 patients treated with CPAP, including those who required IMV, was 11 ± 15 days. As of 23rd May 2020, median duration of hospitalisation for all 23 patients was 15 ± 23 days. Two patients still remain in hospital for rehabilitation and social reasons.

Systemic screening for COVID-19 infection among clinical personnel who looked after those patients was not conducted but we are not aware of any cases of transmission and the hospital data indicate overall a very low infection rate among our staff.

Discussion

In this cohort of middle-aged patients with severe HRF due to COVID-19 pneumonia, CPAP success (avoidance of intubation) was achieved for 61% of patients. To our knowledge this is one of the first studies reporting the effectiveness of CPAP in these patients.

Importantly, we have found no evidence of increased mortality or morbidity associated with IMV among those patients who failed CPAP and required intubation, though most non-responders were intubated within 6 hours of starting CPAP. All patients who required IMV, including the few remaining patients who ended up being intubated >24 hours after starting CPAP (and in one case after 18 days), made satisfactory progress with no difficulties in ventilating or weaning from IMV. This argues against the hypothesis that early intubation, as opposed to a trial of non-invasive support, may offer survival benefit in COVID-19 pneumonia by potentially protecting from self-inflicted or CPAP/NIV induced lung injury. 10

At a mean PaO2/FiO2 of 84.3 mmHg, the level of hypoxaemia in our study was more severe than previously reported in other ICU case series of COVID-19 patients. For instance, in a large Italian cohort of 1287 patients, of whom 88% were treated with IMV and 11% with NIV, the median PaO2/FiO2 ratio was 160 mmHg but it should be noted that those patients were older and had more co-morbidities.2 In an earlier publication from Wuhan, China a median PaO2/FiO2 ratio of 136 mmHg was reported among 36 patients admitted to ICU.11

We found that the application of CPAP doubled the mean PaO2/FiO2 just 1–2 hours into treatment when, in most cases, CPAP was still being titrated. Such substantial and rapid improvement in oxygenation is rarely seen in ARDS and points towards different mechanisms of action than lung recruitment. It is increasingly recognised that whilst most patients with severe COVID-19 pneumonia meet the Berlin definition of ARDS, the pathophysiology of HRF is likely different to that seen in ARDS.12 The profound hypoxaemia seems disproportionate to relatively well preserved respiratory mechanics.13 Unlike in typical ARDS, the majority of patients with COVID-19 pneumonia have near normal lung compliance, at least in the early stages of the disease.14 Hypoxaemia probably occurs predominantly as a result of vascular dysregulation due to endothelial damage caused by the virus and/or inflammation and vascular thrombosis it promotes.15,16 This in turn leads to hyper-perfusion of non-aerated lung regions and ventilation-perfusion mismatch.13 It has been proposed that low levels of PEEP may improve

| Table 2. Comparison of patients who received continuous positive airway pressure therapy with patients treated with supplemental oxygen. |
|---------------------------------------------------------------|
| Age, mean ± SD, years | CPAP therapy (n = 23) | Oxygen therapy (n = 10) | P value |
|-----------------------|------------------------|------------------------|--------|
| BMI, mean ± SD, kg/m² | 54.0 ± 13.9            | 55.0 ± 11.9            | 0.79   |
| PaO2/FiO2 ratio, mean ± SD, mmHg | 84.3 ± 19.0            | 170.0 ± 46.0           | 0.001  |
| RR, mean ± SD, minute⁻¹ | 28 ± 9                | 20 ± 0                 | 0.01   |

Abbreviations: BMI: body mass index; CPAP: continuous positive airway pressure; PaO2/FiO2 ratio: ratio of arterial oxygen partial pressure to fractional inspired oxygen; RR: respiratory rate; SD: standard deviation.
Table 3. Changes in respiratory parameters in response to continuous positive airway pressure therapy (n = 23).

| Parameter                              | Before CPAP       | On CPAP*       | P value  |
|----------------------------------------|-------------------|----------------|----------|
| PaO2/FiO2 ratio, mean ± SD, mmHg       | 84.3 ± 19.0       | 167.4 ± 49.0   | 0.001    |
| RR, mean ± SD, minute⁻¹                | 28 ± 9            | 30 ± 13        | 0.66     |
| pH, mean ± SD                          | 7.48 ± 0.04       | 7.45 ± 0.04    | 0.0001   |
| PaCO2, mean ± SD, mmHg                 | 4.55 ± 0.78       | 4.88 ± 0.83    | 0.001    |

*Based on measurements performed 1–2 hours after CPAP initiation.

Abbreviations: CPAP: continuous positive airway pressure; PaCO2: arterial carbon dioxide partial pressure; PaO2/FiO2 ratio: ratio of arterial oxygen partial pressure to fractional inspired oxygen; RR: respiratory rate; SD: standard deviation.

Table 4. Comparison of respiratory parameters and laboratory biomarkers between continuous positive airway pressure responders and non-responders.

| Parameter                              | CPAP responders (n = 14) | CPAP non-responders (n = 9) | P value |
|----------------------------------------|--------------------------|----------------------------|---------|
| Age, mean ± SD, years                  | 54 ± 12                  | 54 ± 18                    | 0.89    |
| PaO2/FiO2 ratio prior to CPAP therapy, mean ± SD, mmHg | 84.5 ± 16.0 | 83.9 ± 23.0 | 0.94 |
| PaO2/FiO2 ratio change on CPAP therapy, mean ± SD, mmHg | +83.7 ± 43.0 | +82.4 ± 40.0 | 0.95 |
| pH prior to CPAP therapy, mean ± SD    | 7.47 ± 0.03             | 7.49 ± 0.04               | 0.39    |
| pH change on CPAP, mean ± SD           | −0.02 ± 0.02            | −0.04 ± 0.03              | 0.11    |
| PaCO2 prior to CPAP therapy, mean ± SD, mmHg | 4.6 ± 0.66    | 4.4 ± 0.98               | 0.44    |
| PaCO2 change on CPAP, mean ± SD, mmHg  | +0.23 ± 0.4             | +0.51 ± 0.42              | 0.13    |
| RR before CPAP therapy, mean ± SD, minute⁻¹ | 28 ± 9            | 29 ± 4                    | 0.8     |
| RR change on CPAP, mean ± SD, minute⁻¹ | +1.6 ± 7.0           | +0.9 ± 9.1                | 0.84    |
| CRP, mean ± SD, mg/L                   | 176 ± 83               | 274 ± 63                  | 0.01    |
| IL-6, median ± IQR, pg/mL              | 30 ± 47                | 139 ± 148                 | 0.04    |
| D-dimer, median ± IQR, ng/mL           | 321 ± 267              | 941 ± 1990                | 0.001   |
| High sensitivity troponin, median ± IQR, ng/L | 11.0 ± 4.2       | 9.7 ± 34.0                | 0.57    |
| N/L ratio, median ± IQR                | 7.9 ± 10.0             | 8.8 ± 8.9                 | 0.55    |
| Serum ferritin, mean ± SD, ug/L        | 1407 ± 1079            | 1396 ± 1056               | 0.9     |

*Tidal Volume was recorded following CPAP initiation in 13 CPAP responders and 6 non-responders.

Abbreviations: CPAP: continuous positive airway pressure; CRP: C-reactive protein; IL-6: interleukin-6; IQR: interquartile range; N/L: neutrophil/lymphocyte; PaO2/FiO2 ratio: ratio of arterial oxygen partial pressure to fractional inspired oxygen; RR: respiratory rate; SD: standard deviation.

oxygenation by redistributing perfusion to the better aerated lung tissue. For the obese subjects in our cohort, CPAP may have also helped by increasing functional residual capacity above closing capacity and favouring the prevention of small airway closure. The lung recruitment that occurs in ARDS may also be important in later stages of the disease, but it is unlikely to be the main mechanism of CPAP benefit. As such, the evidence from trials that assess the role of CPAP/NIV in ARDS should not be simply extrapolated to COVID-19 pneumonia. Despite improvements in hypoxaemia following application of CPAP, patients typically remained tachypnoeic. This observation may be specific to people with COVID-19 infection who, for not yet well understood reasons, appear to show an increased respiratory drive. We hypothesise that CPAP may be less effective in reducing work of breathing but, in a proportion of patients, the improvement in oxygenation may be sufficient to provide adequate respiratory support and act as a bridge to clinical recovery. The role of an overactive immune response, inflammation and coagulopathy in the disease severity and mortality has gained increasing recognition. Circulating biomarkers associated with inflammation and intravascular coagulopathy have been shown to have prognostic value in multiple studies. In keeping with this, factors which differentiated CPAP responders from non-responders in our study were CRP, IL-6 and D-dimer levels. Although we did not conduct systematic screening for pulmonary thromboembolic disease and thus cannot compare the rate of thrombosis between the two groups, it is noteworthy that among CPAP non-responders 83% (5 out of 6) of patients who underwent CT pulmonary angiogram were diagnosed with pulmonary emboli. This rate is much higher than previously reported in unselected ICU patients with COVID-19 infection. Therefore, it could be hypothesised that the hyperinflammatory state and pulmonary vascular thrombosis contribute to a poor response to CPAP. This is a single centre study from a specialist cardiothoracic centre that had adapted to meet the critical care needs of external hospitals. As such, we recognise unavoidable limitations in the data.
presented. We accepted patients who were judged to require critical care by the referring and receiving clinicians. Patients were transferred from smaller centres that lacked critical care capacity. Those who were transferred to us intubated had not been offered CPAP prior to intubation and therefore are not included in our data. This may skew the unintubated population into a less sick group, although their oxygen requirements on arrival show that they still demonstrated significant physiological compromise. In addition, all patients included were for escalation to intubation and demonstrated lower frailty scores, fewer comorbid conditions and were younger if compared to populations not considered for escalation. In keeping with our local demography, the proportion of patients from black and minority ethnic backgrounds was small. Finally, all patients received continuous monitoring, skilled multidisciplinary input, and staffing that was appropriate for the severity of their condition. Therefore, our findings may not be reproducible in other populations and settings. We present these data to highlight what can be achieved, as this should be the norm for the effective delivery of CPAP in these clinical circumstances. In the UK at least, critical care provision is limited. Delivery of acute CPAP is a skilled procedure and patients require close attention and monitoring with treatment provided by sufficient, trained staff. Inability to provide all aspects of care reduces the effectiveness of non-invasive therapies, and increases the likelihood of failure. 22

Lastly, our sample size is small and therefore some of the statistical analyses presented may have lacked sufficient power to detect significant differences between the groups. However, the magnitude of differences detected in other variables makes them less likely to be due to type I error.

Conclusions
In this study CPAP was a useful treatment modality to avoid invasive mechanical ventilation in a substantial proportion of patients presenting with severe hypoxaemic respiratory failure due to COVID-19 pneumonia. We have found no evidence that CPAP treatment increases morbidity or mortality. Patients who responded to CPAP had lower markers of inflammation and coagulopathy than patients who required tracheal intubation. These findings substantiate the existing evidence for the role of hyperinflammatory response and thrombosis in the severity of the disease and may help in a better risk stratification of patients to the most appropriate respiratory support. Decisions about a trial of CPAP in COVID-19 pneumonia should not be purely based on the respiratory parameters.

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Supplemental material
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