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Early View

Research letter

Continuous positive airway pressure in Covid-19 patients with moderate-to-severe respiratory failure

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Continuous positive airway pressure in Covid-19 patients with moderate-to-severe respiratory failure.

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Introduction

Non-invasive ventilation (NIV) and continuous positive airway pressure (CPAP) are recommended for acute hypoxemic respiratory failure (AHRF) due to cardiogenic pulmonary oedema but no recommendation has been made for viral pandemics, because of lack of randomized studies showing their efficacy and concerns of infection dissemination [1]. Early after Covid-19 outbreak in Italy, there was an expert consensus in favour of CPAP and NIV as first-line treatments for the associated AHRF [2]. However, few studies used unspecified NIV in a minority of patients without detailed results [3–5]. CPAP was the object of two short reports with differing results [6, 7]. Thus, their value in Covid-19 remains to be established.

Two weeks after the outbreak of Covid-19 in our region, we started using systematically CPAP in patients with moderate-to-severe AHRF, following an ad-hoc algorithm. We report here the results obtained in all consecutive patients admitted during the first four weeks after the algorithm implementation. The primary outcome of the study was the 4-week survival without invasive mechanical ventilation (IMV).

Methods

We retrospectively reviewed the records of patients admitted to the Covid-19 unit of the 400-bed Galliera Hospital of Genoa between March 16 and April 12, 2020. Two 20-bed general wards were adapted as sub-intensive units with a filter area for donning and doffing PPEs including N-95. The local ethics committee approved the study (n.5/2020) and waived written consent owing to the observational design.

Ground-glass bilateral pulmonary infiltrates on computed tomography (CT) and positive oropharyngeal swabs for SARS-Cov-2 confirmed Covid-19 pneumonia. Pharmacological treatment included 7-days oral hydroxychloroquine (200 mg) plus methylprednisolone (1 mg/kg) b.i.d, followed by 7-day intravenous anakinra (1,300 mg) or single-dose tocilizumab (8 mg/kg) in case of persistently high inflammatory markers.

Treatment strategy was initially based on arterial oxygen tension to inspired oxygen fraction (PaO_2/FIO_2) on room air, breathing frequency (BF) and presence of dyspnea, and then adjusted following an ad-hoc algorithm (Figure 1A). Patients with pulse oxygen saturation (SpO_2)<95% or PaO_2/FIO_2>200 received oxygen via Ventimask. Criteria for CPAP were PaO_2/FIO_2<200, PaO_2<60 mmHg, BF>30/min, dyspnea at rest or during minimal efforts, if any. IMV was considered after 4 days of unsuccessful CPAP, i.e., with PaO_2/FIO_2 tending to decrease, BF>30/min and PaO_2<60 mmHg.

Three types of Venturi generators were available (EasyVent, EasyFlow, CPAP Flow Generator with Monitor; Dimar, Mirandola, Italy), adapted to deliver outflows of 100-150 L/min with anti-viral filters positioned to both inlet and outlet ports. CPAP was 10 cmH_2O in all patients and FIO_2 40-60% titrated to $PaO_2 \geq 60$ mmHg. During CPAP, patients were in a semi-supine or sitting position. Weaning was started when no desaturation, tachypnea or tachycardia appeared during CPAP interruptions for eating with $PaO_2/FIO_2 > 250$ and tending to increase for two consecutive days at least. During this phase, Ventimask 50% was used over daytime and CPAP overnight. When morning and evening arterial blood gases were comparable, CPAP was ultimately withheld.

CT images (5.00-mm slice thickness) were analysed by ITK-snap software with semi-automatic and manual segmentation of lung parenchyma to calculate lung weight. Categorical variables were compared by Fisher exact test, continuous variables by Mann-Whitney U-test and presented as median with interquartile range (IQR). Factors associated with CPAP failure were first determined by univariate logistic regression analysis, including all anthropometric and clinical data. The variables achieving a $p<0.1$ at univariate analysis were included in a multivariate model analysis. Statistical significance was assumed at two-tailed $P<0.05$.

Results

The total number of patients admitted to hospital with Covid-19 pneumonia over the period considered was of 258 (Figure 1B). Thirteen were directly admitted to the intensive care unit from emergency room or other hospitals, 181 were treated by Ventimask as per algorithm (n=146) or because found ineligible for resuscitation at triage, due to extremely old age or life threatening comorbidities (n=35). Thus, 64 patients underwent CPAP. They had an age range 25-86 yr, had been symptomatic for 7 (IQR 3-10) days. PaO_2/FIO_2 was 119 (IQR 99-153), BF 33/min (IQR 30-38), lung attenuation >-750 HU, and lung weight 1,517 (IQR 1,256-1,870) g. Fifteen of them had been judged ineligible for resuscitation at triage but underwent CPAP thanks to device availability.

Fifty-three (83%) patients recovered with CPAP within 17 days and were dismissed within 28 days. Four patients died under CPAP and seven required IMV. Three of the four patients who died under CPAP and one who died under IMV were among those considered ineligible for resuscitation at triage.

At univariate analysis, odds for CPAP failure were male sex, hypertension, diabetes, chronic obstructive pulmonary disease, having three comorbidities, and lung weight. However, at multivariate analysis, only hypertension remained independently associated with CPAP failure (OR=7.33, 95%C.I. 1.5-34, p=0.012). Baseline PaO_2/FIO_2 tended to be lower (p=0.052), in patients with CPAP failure (Figure

1C) but having PaO_2/FIO_2<150 was insignificant as risk factor, for 36 of the 53 patients recovering with CPAP had PaO_2/FIO_2<150. Lung weight was higher (p=0.031) in subjects with CPAP failure but having lung weight>1.5 kg was insignificant as risk factor, for 23 of the 53 patients recovering with CPAP had lung weight >1.5 kg.

None of staff workers developed signs or symptoms of Covid-19 from the start of this study to the submission date of this manuscript.

Discussion

Our main finding was that the vast majority of Covid-19 patients treated by CPAP recovered from moderate-to-severe AHRF, including cases with gas exchange and radiological findings similar to those considered as indications for IMV in typical adult respiratory distress syndrome (ARDS).

Since the outbreak of Covid-19, the majority of patients with moderate-to-severe AHRF have been treated by IMV, based on subjective judgement or criteria generally used for typical ARDS [8, 9], with 49-60% mortality [3–5]. Early observations in few intubated patients led to postulate that Covid-19 AHRF may differ from typical ARDS for a relatively preserved respiratory mechanics despite similarly severe shunt (PaO_2/FIO_2) and CT abnormalities [10]. Although this has been recently confuted [11], the possibility exists that IMV with high positive end-expiratory pressure may be unnecessary or even harmful in a number of Covid-19 patient and its liberal use should be considered with caution [12, 13]. For the above reasons, we decided to use CPAP in all patients presenting with signs of severe intrapulmonary shunt (PaO_2/FiO_2<200 or PaO_2<60 mmHg on Ventimask 50%) or increased work of breathing (BF>30/min or dyspnea) before considering IMV. In order to maintain the mechanical stress at a minimum and based on prior observations in intubated patients, we set CPAP at 10 cmH_2O in all patients, rather working with high airflow with the aim of reducing BF and dyspnea at the cost of tolerating slight decrements of PaO_2/FIO_2.

The important results of our study are that neither PaO_2/FIO_2 nor lung weight were predictors of CPAP failure. In particular, CPAP avoided death or intubation in 36 out of 53 patients with PaO_2/FIO_2<150 and/or lung weight >1.5 Kg, which are usually considered as indications for IMV in typical ARDS [9]. In particular, PaO_2/FIO_2<150 was in a large multicentre study comparing NIV with IMV in typical ARDS, associated with higher mortality [14]. Although we obtained favourable results with CPAP also in patients meeting the criteria of severe ARDS, we cannot say whether this was due to Covid-19 AHRF differing from other forms of ARDS.

In Covid-19 AHRF, few studies reported occasional use of NIV [3, 4, 15] without giving technical details or selection criteria and only one [5] considered the mortality of NIV separately from IMV without finding a statistically significant difference. More recently, two research letters reported on CPAP. Oranger et al. [6], using high-end home mechanical ventilators, found that CPAP avoided intubation in about three fourths of patients, but there was no information to relate outcomes to severity of respiratory failure or CT imaging. Aliberti et al. [7], using helmets with high-flow generators, found that CPAP avoided intubation in only about half of patients. A possible explanation for higher CPAP success in our study is a difference in criteria for intubation.

Limitations of the present study are the retrospective nature without comparator group, the single-centre and the small sample size, which limits the generalizability of results regarding risk factors and effects of pharmacological treatments.

In conclusion, our results suggest that a number of patients with moderate-to-severe AHRF due to Covid-19 pneumonia may be amenable to high-flow CPAP, even in the presence of gas exchange and CT findings usually considered as indications for IMV or even extracorporeal oxygenation in typical ARDS.

Author contributions

Drs Brusasco C and Corradi contributed to the study design, data collection and analysis, and the writing of the manuscript and are the guarantor of the paper, *Dr Raggi and Timossi* contributed to the data collection, data analysis, reading and checking of the manuscript, *Dr Di Domenico* contributed as data manager, building of the database, data analysis, reading and checking of the manuscript, *Dr Santori* contributed to statistical analysis, data results analysis, reading and checking of the manuscript, *Prof Brusasco V* contributed to the study design, data results interpretation and writing of the manuscript.

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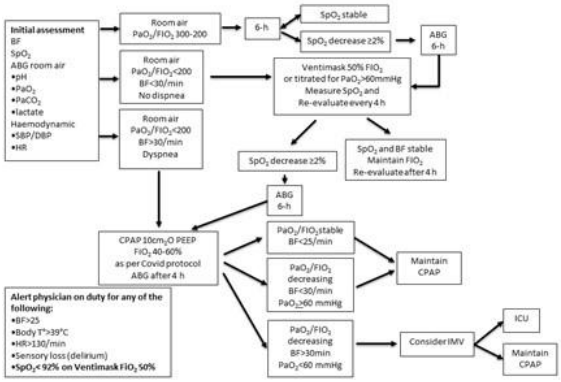
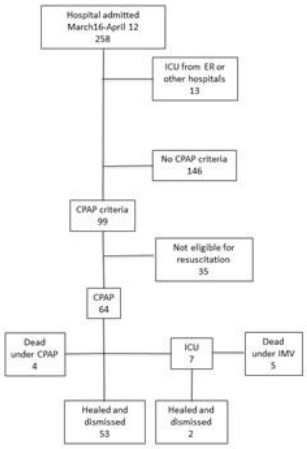
Figure legends

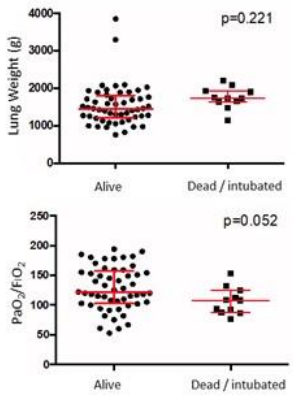
Figure 1. *Panel A.* Algorithm for respiratory support to Covid-19 patients. BF, breathing frequency; ABG, arterial blood gas; PaO_2/FIO_2, ratio of arterial oxygen pressure to inspired oxygen fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; CPAP, non-invasive ventilation in continuous positive airway pressure mode; IMV, invasive mechanical ventilation; ICU, intensive care unit. *Panel B.* Study diagram. ICU, intensive care unit; ER, emergency room; DNR, do not resuscitate order; CPAP, continuous positive airway pressure mode. *Panel C.* Scatterplots of individual values of CT-estimated lung weight (left) and PaO_2/FIO_2 (right), with medians and interquartile ranges.


Initial assessment
BF
SpO2
ABG room air
•pH
•PaO2
•PaCO2
•lactate
Haemodynamic
•SBP/DBP
•HR
Room air
PaO2/FIO2 300-200
6-h
SpO2 stable
SpO2 decrease ≥2%
ABG
6-h
Room air
PaO2/FIO2<200
BF<30/min
No dispnea
Ventimask 50% FIO2
or titrated for PaO2>60mmHg
Measure SpO2 and
Re-evaluate every 4 h
Room air
PaO2/FIO2<200
BF>30/min
Dyspnea
SpO2 decrease ≥2%
SpO2 and BF stable
Maintain FIO2
Re-evaluate after 4 h
ABG
6-h
CPAP 10cmH2O PEEP
FIO2 40-60%
as per Covid protocol
ABG after 4 h
PaO2/FIO2 stable
BF<25/min
PaO2/FIO2
decreasing
BF<30/min
PaO2>60 mmHg
PaO2/FIO2
decreasing
BF>30min
PaO2<60 mmHg
Maintain
CPAP
Consider IMV
ICU
Maintain
CPAP
Alert physician on duty for any of the following:
•BF>25
•Body T°>39°C
•HR>130/min
•Sensory loss (delirium)
•SpO2< 92% on Ventimask FIO2 50%

A


Hospital admitted
March16-April 12
258
ICU from ER or
other hospitals
13
No CPAP criteria
146
CPAP criteria
99
Not eligible for
resuscitation
35
CPAP
64
Dead
under CPAP
4
ICU
7
Dead
under IMV
5
Healed and
dismissed
53
Healed and
dismissed
2

B


Lung Weight (g)
4000
3000
2000
1000
0
p=0.221
Alive
Dead / intubated
PaO2/FiO2
250
200
150
100
50
0
p=0.052
Alive
Dead / intubated

C