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[Research Letter]

CHEST

Prone and Lateral Positioning in Spontaneously Breathing Patients With COVID-19 Pneumonia Undergoing Noninvasive Helmet CPAP Treatment

To the Editor:

Patients with coronavirus disease 2019 (COVID-19) pneumonia can experience the development of hypoxemic acute respiratory failure (hARF) that might require the application of a positive end-expiratory pressure (PEEP).[1] CPAP improves oxygenation and reduces the need for endotracheal intubation in comparison with standard oxygen therapy in patients with severe hARF due to pneumonia.[2,3] During CPAP treatment, patients with hARF might also benefit of additional interventions, such as prone positioning.[4] Pronation of awake, spontaneously breathing, nonintubated patients with hARF is feasible, safe, and associated with a significant benefit on oxygenation.[5,6] Lateral position may be also associated with beneficial effects on gas exchange, especially in unilateral widespread infiltrates.[7] Finally, a recent experience demonstrated that awake, early self-proning improves oxygen saturation in patients with COVID-19.[8] The objective of this study was to evaluate the efficacy of both prone and lateral positioning in patients who undergo helmet CPAP because of hARF that is caused by COVID-19 pneumonia.

Methods

A pilot, observational, prospective study was conducted at the COVID-19 respiratory high-dependency unit (HDU) of the Policlinico Hospital in Milan, Italy, between March and April 2020. The respiratory HDU is characterized by a nurse:patient ratio per shift of 1:4, multivariable monitors, noninvasive ventilators, and life support, on-site intubation and invasive ventilation, attending physicians available 24 hours 7 days a week, and bronchoscopy and arterial blood gas analysis inside the unit.[9] Consecutively recruited adults (≥18 years old) with hARF caused by laboratory-confirmed COVID-19 pneumonia who were undergoing helmet CPAP treatment were included in this study. All patients who were undergoing helmet CPAP had a Glasgow Coma Scale of 15 and were spontaneously breathing and not intubated. The Institutional Review Board of the Policlinico hospital approved the study (#345_2020). Patients with at least one of the following criteria were excluded: need for immediate intubation, Glasgow Coma Scale <15, systolic BP (SBP) < 90 mm Hg, and SpO_2 <90% at FIO_2 >0.8. Patients underwent either prone or lateral positioning according to standard operating procedures and the last chest radiograph or chest CT scan. A trial of prone/lateral position was started as an intervention in patients with COVID-19 who were undergoing helmet CPAP if their PaO_2:FIO_2 ratio that had been evaluated during helmet CPAP treatment was persistently <250 after at least 48 hours. Lateral position was performed when lung impairment was mainly monolateral, with the lung with no or less involvement placed down, whereas prone position was adopted when lung impairment was bilateral (Fig 1A and B.[10] Prone/lateral position lasted 1 hour. Levels of both PEEP and FIO_2 did not change during the trial and were selected as per clinical indication. Vital parameters and blood gas analysis were recorded at three time points: before the trial with the patient in a semi-seated position (T0), after 1 hour from trial initiation with the patient in prone/lateral position (T1), and 45 minutes after the trial with the patient returned to a semi-seated position (T2). The primary outcome was the success of the prone/lateral positioning trial, defined as the occurrence of all of the following criteria at T1 in comparison with T0: (1) a decrease of the alveolar–arterial gradient (A-aO_2) of at least 20%, (2) equal or reduced respiratory rate, (3) equal or reduced dyspnea (evaluated through the BORG scale), and (4) SBP ≥90 mm Hg. Trial failure was defined as the occurrence of at least one of the following criteria during the test: (1) an unchanged or increased A-aO_2; (2) an increased respiratory rate, (3) a decrease of SBP <90 mm Hg, (4) a SpO_2 <90%, (5) occurrence of respiratory distress, and (6) occurrence of patient's discomfort.Qualitative variables were described with absolute and relative (percentage) frequencies, whereas quantitative variables were summarized with means (SD) or medians (interquartile ranges [IQR]) in the case of parametric or nonparametric distribution, respectively. Analysis of variance and Friedman tests were used to detect any statistical differences in the comparison of normal and nonnormal vital and blood gas analysis parameters during different time points. A two-tailed probability value of <.05 was considered statistically significant. The statistical software STATA (version 16; (StataCorp, College Station, TX) was used to perform all statistical computations.

Results

A total of 26 patients (67% male; median age: 62 year [IQR, 56-69 years] were included. The most prevalent comorbidities were systemic hypertension (43%), diabetes mellitus (21%), obesity (14%), COPD (11%), and asthma (11%). On HDU admission, the median

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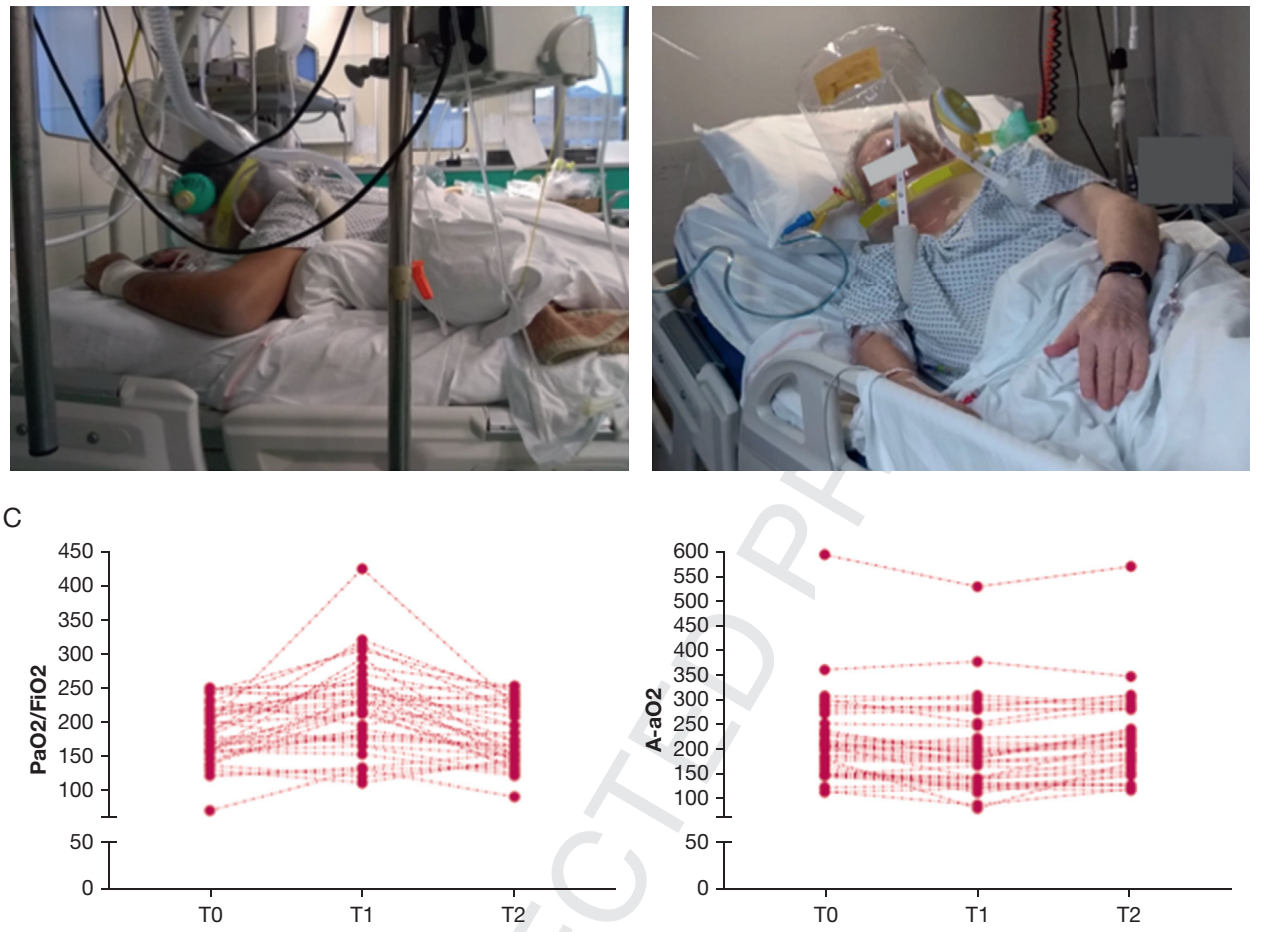

Figure 1 – *A, Prone and B, lateral positioning during helmet CPAP treatment. C, Changes in Pa_{O_2}:F_{IO_2} ratio and A-a_{O_2} before (T0), after one hour during the test (T1), and after the test (T2) in the overall study population.*

PaO_2:FiO_2 ratio on oxygen therapy delivered through Venturi mask was 143 (IQR, 97-204); the A-a_{O_2} was 269 ●●●● (IQR, 144-540●●●●), and the respiratory rate was 27 beats/min (IQR, 22-31 beats/min). All patients had hARF that was caused by COVID-19 pneumonia and who underwent helmet CPAP with a median Pa_{O_2}:F_{IO_2} ratio of 180 (IQR, 155-218) and A-a_{O_2} of 207 (156-262). A total of 39 tests (12 prone and 27 lateral positioning) were conducted after a median time from symptoms onset of 14 days (IQR, 10-17 days) and of 4 days (IQR, 2-7 days) from HDU admission. All tests but two (both in lateral positioning due to patient discomfort) were carried out. Changing of vital parameters and blood gas analysis values before, during, and after the test are reported in Table 1 and Figure 1C for all patients who completed the trial. In terms of primary end point, 6 trials (15.4%) were successful with a decrease of A-a_{O_2} of 20% during the trial or more in comparison with baseline. Three trials (7.7%) showed a A-a_{O_2} decrease of at least 30% in comparison with baseline values.

Seventeen trials (46.1%) showed a decrease of <20% of A-a_{O_2}. A total of 15 trials (38.5%) failed: one patient (2.6%) experienced a decrease of SBP (<90 mm Hg); two patients experienced discomfort (5.1%); three patients (7.7%) had an increase in respiratory rate, and nine patients (23.1%) had an increase of A-a_{O_2}. Among trials conducted in prone positioning, 33.3% succeeded; 41.7% showed a decreased A-a_{O_2} (<20%), whereas 25% failed. Among trials conducted in lateral positioning, 8% succeeded; 52% showed a decrease of A-a_{O_2} (<20%), while 40% failed. Improved gas exchange that was achieved during the trial reverted, returning to the semiseated position (Table 1). Seven of 26 patients (26.9%) underwent intubation and were mechanically ventilated; two patients (7.7%) died.

Discussion

The main study findings were (1) that only a small proportion of prone/lateral positioning tests conducted in patients with COVID-19 on helmet CPAP therapy

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TABLE 1] Changes in Vital Parameters and Blood Gas Analysis Before the Test, After One Hour During the Test, and After the Test in the Overall Study Population and Among Those Who Underwent Either Prone or Lateral Positioning

Variable	Before the Test	During the Test	After the Test	*P* Value[a]	*P* Value[b]
Overall population					
Vitals					
Systolic BP, mean (SD), mm Hg	124.4 (18.8)	122.7 (16.8)	123.0 (13.9)	1.00	.89
Diastolic BP, mean (SD), mm Hg	73.7 (12.4)	71.8 (11.9)	72.9 (9.5)	1.00	.77
Heart rate, mean (SD), beats/min	75.4 (12.6)	77.2 (12.2)	72.5 (15.1)	1.00	.32
Respiratory rate, mean (SD), beats/min	23.7 (4.7)	23.1 (4.5)	23.6 (4.7)	1.00	.80
SpO_2, median (IQR), %	96 (95-98)	98 (97-98)	97 (95-98)	<.0001	<.0001
Blood gas analysis					
pH, mean (SD)	7.45 (0.03)	7.45 (0.02)	7.45 (0.03)	1.00	.69
$Paco_2$, median (IQR), mm Hg	38 (35-40)	38 (35-39)	38 (35-40)	.69	.36
Pao_2, mean (SD), mm Hg	86.9 (15.1)	104.5 (25.0)	85.4 (13.4)	<.0001	<.0001
Pao_2:Fio_2 ratio, mean (SD)	182.9 (43.0)	220.0 (64.5)	179.3 (43.9)	.008	.002
A-ao_2, median (IQR)	207.1 (160.7-251.3)	184.3 (141.4-246.8)	209.5 (153.5-282.3)	.0002	.0002
Prone positioning (n = 12)					
Vitals					
Systolic BP, mean (SD), mm Hg	122.8 (13.3)	124.3 (14.9)	125 (12.7)	1.00	.92
Diastolic BP, mean (SD), mm Hg	72.3 (10.1)	72.7 (11.7)	73.6 (8.8)	1.00	.95
Heart rate, mean (SD), beats/min	76.6 (14.2)	76.9 (11.7)	71.6 (13.6)	1.00	.56
Respiratory rate, mean (SD), beats/min	23.5 (6.3)	21.3 (5.0)	22.9 (6.0)	1.00	.62
SpO_2, median (IQR), %	95 (93.5-96.0)	98 (98-99)	96 (95-98)	<.0001	<.0001
Blood gas analysis					
pH, mean (SD)	7.46 (0.02)	7.46 (0.02)	7.45 (0.04)	1.00	.77
$Paco_2$, median (IQR), mm Hg	39 (35.5-40.5)	38 (34.5-41.0)	37 (35-41)	1.00	.74
Pao_2, mean (SD), mm Hg	83.6 (14.2)	112.3 (32.3)	85.6 (11.5)	.008	.004
Pao_2:Fio_2 ratio, mean (SD)	168.7 (46.2)	227.7 (90.3)	166.9 (45.3)	.10	.046
A-ao_2, median (IQR)	219.3 (183.2-279.8)	193.1 (132.3-281.2)	229.3 (173.6-292.8)	.03	.02
Lateral positioning (n = 25)					
Vitals					
Systolic BP, mean (SD), mm Hg	125.2 (21.2)	121.9 (17.9)	122 (14.6)	1.00	.77
Diastolic BP, mean (SD), mm Hg	74.4 (13.5)	71.4 (12.3)	72.5 (9.9)	1.00	.67
Heart rate, mean (SD), beats/min	74.8 (12.0)	77.4 (12.7)	72.9 (16.0)	1.00	.53
Respiratory rate, mean (SD), beats/min	23.8 (.9)	23.9 (4.0)	24.0 (4.1)	1.00	1.00
SpO_2, median (IQR), %	97 (96-98)	98 (96-98)	97 (96-98)	.03	.09
Blood gas analysis					
pH, mean (SD)	7.46 (0.03)	7.45 (0.02)	7.45 (0.02)	1.00	.88
$Paco_2$, median (IQR), mm Hg	38 (34-39)	37 (35-39)	38 (35-40)	.62	.07
Pao_2, mean (SD), mm Hg	88.4 (15.5)	100.8 (20.4)	85.8 (14.5)	.04	.006
Pao_2:Fio_2 ratio, mean (SD)	189.7 (40.6)	216.2 (49.6)	185.0 (43.0	.11	.04
A-ao_2, median (IQR)	198.8 (151.7-227.8)	182.8 (142.0-213.8)	199 (153.3-260.6)	.003	.007

IQR = interquartile range; SpO_2 = oxygen saturation level.
[a]Before the test vs after one hour during the test.
[b]Among the three groups.

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succeeded (significant improvement of gas exchange), (2) that the decrease of the A-aO_2 was <20% (minimum clinically relevant important difference), (3) that there was a higher success rate in prone positioning vs lateral positioning, and (4) that the improved gas exchange changed when the patient returned to the semi-seated position.

The A-aO_2 gradient was adopted as the end point because of the COVID-19 pneumonia-related ARF. A-aO_2 gradient can better assess gas exchange dysfunction in comparison with PaO_2:FIO_2 ratio being patients hypocapnic. The 20% threshold for A-aO_2 gradient decrease as a component of the primary outcome was chosen arbitrarily by the study team after consensus that considered previously published literature on prone positioning.[11] Notably, from 25% (prone positioning) to 40% (lateral positioning) of the tests failed, because of an increase of respiratory rate or A-aO_2. Physicians should be aware of strict monitoring by expert respiratory physiotherapists or nurses during prone/lateral positioning. The relatively high failure rate might be related mainly to the complex pathophysiology of respiratory failure in patients with COVID-19, where diffuse alveolar damage (like in "classic" ARDS) and diffuse endothelial damage that leads to pulmonary intravascular coagulopathy with disseminated microthrombosis were found.

This study has several limitations. First, it was designed as a "purely physiologic" study, without assessment of the potential impact of prone/lateral positioning on clinical outcomes or confounders, such as setting (eg, FIO_2 and PEEP) and length of CPAP treatment before the trial. Further randomized controlled trials are needed to evaluate the efficacy of prone/lateral positioning on both intubation and mortality rate. Second, we evaluated both response and tolerance only after one hour since test initiation. Different studies showed that a positive response of patients with ARDS can be recorded several hours after having turned the patient prone and that long-term information about tolerance and compliance to prone positioning are needed because they might impact clinical outcomes. This is the first experience of prone/lateral positioning in awake, spontaneously breathing patients with COVID-19 who were treated with helmet CPAP. Our results could help design multicenter randomized controlled trials on prone/lateral positioning in nonintubated patients with COVID-19.

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References

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497-506.
2. Cosentini R, Brambilla AM, Aliberti S, et al. Helmet continous positive airway pressure vs oxygen therapy to improve oxygentaion in community-acquires pneumonia: a randomized controlled trial. *Chest*. 2010;138(1):114-120.
3. Brambilla AM, Aliberti S, Prina E, et al. Helmet CPAP vs oxygen therapy in severe hypoxemic respiratory failure due to pneumonia. *Intensive Care Med*. 2014;40(7):942-949.
4. Gattinoni L, Busana M, Giosa L, Macrì MM, Quintel M. Prone positioning in acute respiratory distress syndrome. *Semin Respir Crit Care Med*. 2019;40(1):94-100.
5. Scaravilli V, Grasselli G, Castagna L, et al. Prone positioning improves oxygenation in spontaneously breathing nonintubated patients with hypoxemic acute respiratory failure: a retrospective study. *J Crit Care*. 2015;30(6):1390-1394.
6. Ding L, Wang L, Ma W, He H. Efficacy and safety of early prone positioning combined with HFNC or NIV in moderate to severe

ARDS: a multi-center prospective cohort study. *Crit Care*. 2020;24(1):28.

7. Hewitt N, Bucknall T, Faraone NM. Lateral positioning for critically ill adult patients. *Cochrane Database Syst Rev*. 2016;●●●●(5): CD007205.
8. Caputo ND, Strayer RJ, Levitan R. Early self-proning in awake, non-intubated patients in the emergency department: a single ED's experience during the COVID-19 pandemic. *Acad Emerg Med*. 2020;27(5):375-378.
9. Scala R, Corrado A, Confalonieri M, Marchese S, Ambrosino N; Scientific Group on Respiratory Intensive Care of the Italian Association of Hospital Pneumologists. Increased number and expertise of Italian respiratory high-dependency care units: the second national survey. *Respir Care*. 2011;56(8):1100-1107.
10. Yeaw EM. How position affects oxygenation. Good lung down? *Am J Nurs*. 1992;92(3):26-29.
11. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013;368(23):2159-2168.

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