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Prone position in non-intubated patients with COVID-19 related acute respiratory failure

La pronazione nei pazienti non intubati con insufficienza respiratoria acuta da COVID-19

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Summary

Background. Although pronation is mostly used as a treatment option in intubated patients with severe acute respiratory distress syndrome (ARDS), COVID-19 health emergency has led to a revaluation of this technique also in patients undergoing non-invasive ventilation (NIV).

Objectives. The main study outcome was to assess oxygenation level for patients kept in prone position by comparing partial pressure of oxygen on fractional concentration of oxygen in inspired air (PO_2/FiO_2 ratio) changes before pronation and one hour after resupination.

Method. In this retrospective single centre study, 20 patients over 18 years with a confirmed diagnosis of COVID-19 related pneumonia and receiving helmet-CPAP or NIV were enrolled from Villa Scassi Hospital (Genoa, Italy) between March and May 2020. Data regarding blood gas measurements, respiratory rate and dyspnoea severity were collected immediately before pronation (T0), during pronation (T1) and one hour after resupination (T2). Patients were responding if their PO_2/FiO_2 ratio had improved by at least 20% comparing T0 and T2.

Results. In patients undergoing helmet-CPAP the PO_2/FiO_2 ratio improved significantly comparing data at T0 and T1 (p-value < 0.0001) and even when the supine position was resumed (p-value < 0.0001). The slopes of PO_2/FiO_2 ratio from T0 and T1 between the two groups of responders and not-responders also differed significantly (p-value = 0.004).

Discussion. Our results show that pronation improves oxygenation in awake patients with COVID-19-related pneumonia receiving helmet-CPAP, and this effect is maintained even one hour after re-supination. The significant difference in the slope of the PO_2/FiO_2 ratio from T0 and T1 between the two groups shows that a lack of substantial increase in the ratio between supine and prone position could predict a failure of this technique.

Conclusions. In a health emergency such a global pandemic where available resources are limited, pronation should always be attempted in patients with COVID-19 pneumonia in ARDS undergoing helmet-CPAP.

Key words: prone position, non-invasive ventilation, ARDS, SARS-CoV-2

Riassunto

Background. *Sebbene la pronazione sia utilizzata principalmente come trattamento nei pazienti intubati con sindrome da distress respiratorio acuto grave (ARDS), l'emergenza sanitaria COVID-19 ha portato ad una rivalutazione di questa tecnica anche nei pazienti sottoposti a ventilazione non invasiva (NIV).*

Obiettivi. *Il risultato principale dello studio è stato valutare il livello di ossigenazione dei pazienti sottoposti a pronazione confrontando la pressione parziale di ossigeno sulla concentrazione frazionaria di ossigeno nell'aria inspirata (rapporto PO_2/FiO_2) prima della pronazione e un'ora dopo la re-supinazione.*

Materiali e metodi. *In questo studio retrospettivo monocentrico condotto presso l'Ospedale Villa Scassi (Genova, Italia) tra Marzo e Maggio 2020 sono stati arruolati 20 pazienti maggiorenni sottoposti a casco-CPAP o NIV con diagnosi confermata di polmonite COVID-19. I dati relativi alle misurazioni dei gas ematici, la frequenza respiratoria e la dispnea sono stati*

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Conflict of interest statement
The Authors declare no conflict of interest.

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raccolti immediatamente prima della pronazione (T0), durante la pronazione (T1) e un'ora dopo la resupinazione (T2). I pazienti sono stati definiti responders se il rapporto PO_2/FiO_2 migliorava di almeno il 20% confrontando T0 e T2.
Risultati. *Nei pazienti sottoposti a casco-CPAP il rapporto PO_2/FiO_2 è migliorato in maniera significativa tra T0 e T1 ($p < 0,0001$) e anche quando è stata ripristinata la posizione supina ($p < 0,0001$). Le pendenze del rapporto PO_2/FiO_2 da T0 e T1 tra i due gruppi di responders e non-responders differivano significativamente ($p = 0,004$).*
Discussione. *La pronazione migliora l'ossigenazione nei pazienti con polmonite COVID-19 in casco-CPAP e questo effetto si mantiene anche un'ora dopo la re-supinazione. La significativa differenza nella pendenza del rapporto PO_2/FiO_2 da T0 e T1 tra i due gruppi mostra che una mancanza di sostanziale aumento del rapporto tra posizione supina e prona potrebbe predire un fallimento di questa tecnica.*
Conclusioni. *In un'emergenza sanitaria come una pandemia con risorse limitate, la pronazione dovrebbe sempre essere tentata nei pazienti con polmonite COVID-19 in ARDS sottoposti a casco-CPAP.*

Parole chiave: *posizione prona, ventilazione non invasiva, ARDS, SARS-CoV-2*

Introduction

During prone position, alveolar inflation is more uniform than in supine position; this effect leads to a more homogeneous distribution of ventilation-perfusion ratio and of any eventual lung injury inflicted by ventilation [1]. A multicenter study conducted in 2013 by Guarin et al. and the following works show that early pronation of selected patients with severe ARDS for at least 16 h/day improves survival [2-5]. Some studies have been conducted in patients undergoing non-invasive ventilation (NIV) in prone position. Earlier this year Ding et al. found that early application of pronation in patients with moderate ARDS and treated with high flow nasal cannula (HFNC) or NIV can avoid intubation [6]. Although the Surviving Sepsis Campaign initially recommended treating COVID-19 pneumonia like ARDS [7], there are some pathophysiological differences between classic ARDS and COVID-19 pneumonia: as Gattinioni described, in phenotype 1 disease the compliance of the lung is still preserved with a relatively low lung weight and hypoxemia can be mostly explained by a disfunction of mechanism of hypoxic vessel-constriction [8]. During a global pandemic where available resources are limited and intensive care units overloaded, the use of prone position may be impactful to improve oxygenation and to prevent the risk of intubation. So far, only few studies involving small samples have been conducted on pronation in spontaneously breathing patients with SARS-CoV-2 infection [9-12], and there is agreement that more research is needed. Some Scientific Societies have provided the first recommendations, defining both the right setting and the patients who could benefit from this technique [13-15].

The objective of this study was to evaluate the use of prone position in non-intubated patients with ARDS secondary to a SARS-CoV-2 infection and its effect on oxygenation through the variation of the PO_2/FiO_2 ratio between the initial supine position (T0) and one hour after from resupination (T2).

Materials and methods

In this a single-centre retrospective clinical study, we enrolled patients with SARS-CoV-2 pneumonia admitted to Pneumology Department of Villa Scassi Hospital in Genoa, Italy, between March and May 2020. Data were collected retrospectively and stored anonymously through the hospital's SIVIS electronic system. Patients were eligible for inclusion if they were aged over 18 years, had a bilateral interstitial pneumonia shown by an chest X-ray or computer tomography (CT), with a documented SARS-CoV-2 infection from at least one positive RT-PCR nasal swab. All included patients had an ARDS (defined according to the Berlin classification) with PO_2/FiO_2 ratio < 250 in non-invasive ventilation; this cut off has been established in agreement with anesthesiologists considering this manoeuvre as a rescue treatment for patients with moderate or severe ARDS. All patients provided written informed consent to treatment. Patients were excluded if they had a stable PO_2/FiO_2 ratio > 250, contraindications to pronation, lack of compliance to pronation, or were candidate for intubation. Personal and demographic data such as smoking habits, history of allergies, presence of comorbidities (obesity, COPD, asthma, diabetes, hypertension), use of drugs (steroids, heparin, antibiotics, hydroxychloroquine, antivirals, tocilizumab), days of hospitalization, ventilation strategy, need for intubation, death, blood tests (interleukin-6, ferritin, creatine-kinase, lactic dehydrogenase, C-reactive protein, procalcitonin, D-dimer) were collected. Not-hypercapnic patients received ventilation through helmet-CPAP; for patients with hypercapnia, we used NIV in Bi-level mode. For each individual patient, the same ventilation strategy, the same FiO_2 and positive end-expiratory pressure (PEEP) were maintained before, during pronation and one hour after re-supination. Data regarding blood gas measurements, respiratory rate and dyspnoea severity, expressed by the Borg Scale, were collected immediately before pronation (T0), during pronation (T1) and one hour after resupination (T2). Pronation was performed with nursing help which encouraged patients to maintain prone position for at least three hours three times a day, assuming temporary lateral decubitus position if poorly tolerated. Patients could decide whether to sleep or to remain awake. Vital signs such as saturation, blood pressure and heart rate were monitored during the entire duration of the manoeuvre, at one-hour intervals. The primary outcome was the assessment of oxygenation, determined through the change of the PO_2/FiO_2 ratio between the time points T0 and T2. Patients were classified as "responders" if their PO_2/FiO_2 ratio had increased of at least 20% from T0 to T2. Secondary outcomes were the effect of prone position on partial pressure oxygen, respiratory rate, dyspnoea severity, and differences in PO_2/FiO_2 ratio curve slope from timepoints T0 and T1 and in blood tests between responders and not-responders.

Statistical analyses

The two-sample Kolmogorov-Smirnov (KS) test [16,17] was used to compare the various distributions at different time points, and also to compare responders and non-responders; the test statistics D indicates the maximum deviation between the two cumulative distributions to compare. A p-value < 0.05 was considered statistically significant. All the analyses were conducted using the statistical software R version 4.0.2 [18].

Results

Between March and May 2020, 84 patients were admitted to the Pneumology Department of Villa Scassi Hospital in Genoa, Italy, due to a SARS-CoV-2 pneumonia; among them, 63 patients did not fulfil our inclusion criteria. At first, 21 patients eligible for prone position were included in this study; one of them was afterwards excluded due to poor collaboration. Thus, 20 patients were enrolled in the final cohort. Shown in Table I we find the main characteristics of the study population. All patients maintained prone position for at least four hours and no significant side effects or complications were observed. Shown in Table II we find the ventilation parameters, arterial blood gas measurements of PO_2/FiO_2 and PO_2, respiratory rate and dyspnoea severity degree of the 20 patients at the three timepoints considered, T0 (in the supine position), T1 (during pronation) and T2 (one hour after re-supination). On average, the PO_2/FiO_2 ratio improved significantly when comparing T0 and T1 ($D = 0.8$, p-value < 0.0001); the improvement remained significant even when the supine position was resumed (difference T0 vs T2 $D = 0.8$, p-value < 0.0001). The partial pressure of oxygen improved significantly from T0 to T1 ($D = 0.8$, p-value < 0.0001); for this parameter the improvement remained significant even after re-supination ($D = 0.65$, p-value $= 0.0004$). Pronation significantly decreased the respiratory rate in comparison to supine position ($D = 0.55$, p-value $= 0.005$). Each patient PO_2/FiO_2 ratio change from T0 to T1 and T2 is shown in Figure 1. We classified as responders the 16 patients with an increased PO_2/FiO_2 ratio ≥ 20% from T0 to T2; the remaining 4 patients were considered as not responders because of a PO_2/FiO_2 ratio variation < 20%. As shown in Figure 2, there is a statistically significant difference between responders and non-responders when comparing the distribution of their curve slope of PO_2/FiO_2 ratio at T0 and T1 ($D = 1$, p-value $= 0.004$). Comparing

Table I. Main characteristics of the study population.

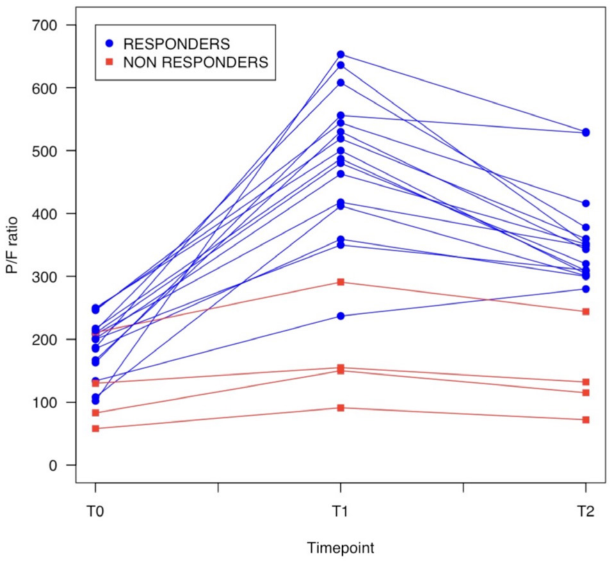
Mean age, years	59.5 (12.2)
Female	5 (25%)
Male	15 (75%)
Hospitalization, days	37.3 (15.9)
Allergies	4 (20%)
Smokers	4 (20%)
Not smokers	16 (80%)
Comorbidities	
Obesity	4 (20%)
COPD	2 (10%)
Asthma	0 (0%)
Diabetes	5 (25%)
Hypertension	6 (30%)
Drugs	
Antibiotics	20 (100%)
Steroids	20 (100%)
Heparin	20 (100%)
Hydroxychloroquine	19 (95%)
Antivirals	7 (35%)
Tocilizumab	10 (50%)
Ventilation strategy	
CPAP Helmet	19 (95%)
NIV Bi-level	1 (5%)
Intubated	4 (20%)
Survivors	17 (85%)
Dead	3 (15%)
Blood tests	
Interleukin-6	289.4 (561)
Ferritin	1338.6 (945.5)
Lactic dehydrogenase	380.7 (127.6)
D-Dimer	6793.7 (10449)
Creatine-kinase	171.2 (150.9)
C-reactive protein	119.4 (83.8)
Procalcitonin	0.39 (0.74)

Data are n (%) or means (SD). COPD: chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; NIV: non-invasive ventilation

Table II. Ventilation parameters, arterial blood gas measurements, respiratory rate and dyspnoea severity degree of the 20 patients during the three timepoints, T0, T1 and T2.

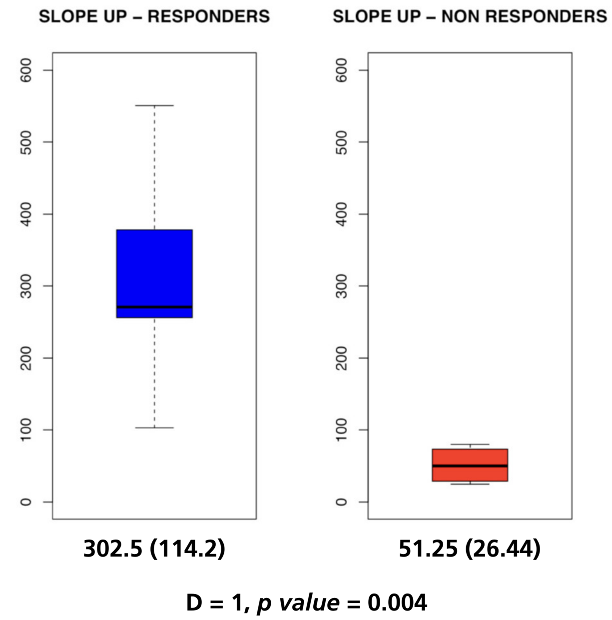
	T0	T1	T2	T0 *vs* T1		T0 *vs* T2	
				D	*p value*	D	*p value*
FiO_2 %	74 (16.6)	74 (16.6)	74 (16.6)				
PEEP cm H_2O	13.5 (3.8)	13.5 (3.8)	13.5 (3.8)				
PO_2/FiO_2 ratio	176.1 (56.3)	421.95 (165.1)	314.6 (115.1)	0.8	**< 0.0001**	0.8	**< 0.0001**
PO_2 mmHg	126.7 (44.5)	295 (111.2)	222.2 (76.5)	0.8	**< 0.0001**	0.65	**0.0004**
RR	25.1 (3.4)	22.1 (3.3)	23.5 (3.8)	0.55	**0.005**	0.35	0.17
Dyspnoea	4.3 (2.3)	2.8 (2.3)	3.3 (2.4)	0.4	0.08	0.3	0.33

Data are means (DS). D e p value were calculated using Kolmogorov-Smirnov test. T0: baseline supine position; T1: during prone position; T2: 1 h after resupinaton; FiO_2: fractional concentration of oxygen in inspired air; PEEP: positive end-expiratory pressure; PO_2: partial pressure of oxygen; RR: respiratory rate.



T0: baseline supine position; T1: during prone position; T2: 1 h after resupinaton; FiO_2: fractional concentration of oxygen in inspired air; PO_2: partial pressure of oxygen. Responders were defined as patients with an increased PO_2/FiO_2 ratio ≥ 20% from T0 to T2.

Figure 1. PO_2/FiO_2 ratio change for each individual patients during the three timepoints T0, T1, T2.



Data are means (DS). D e p value were calculated using Kolmogorov-Smirnov test.

Figure 2. Comparison of the PO_2/FiO_2 ratio curve slope from T0 and T1 between responders and not responders.

baseline blood tests between patients who responded to pronation with those who did not, no statistically significant differences were identified between the two groups. No cases of infectious transmission between patients and healthcare staff were recorded.

Discussion

In our study we found that pronation improves oxygenation in awake patients with COVID-19-related pneumonia requiring helmet-CPAP, and this effect is maintained even after one hour of re-supination in most patients. Our data are in line with the conclusions of the study conducted by Sartini et al. showing that oxygenation improved during pronation and remained stable even one hour after resupination in 15 patients with COVID-19 pneumonia and severe ARDS undergoing NIV [11]. In a recent study on awake patients with SARS-CoV-2 infection in oxygen therapy at a New York Emergency Department, the median oxygen saturation (SO_2) improved from 84% to 94% thanks to the prone position [12]. According to Thomson, the use of prone position was associated with better oxygenation in awake patients in spontaneous breathing with severe COVID-19 hypoxemic respiratory failure; in addition, patients with an SO_2 ≥ 95% after one hour of pronation had a lower intubation rate [19]. By contrast, Elharrar and colleagues found that oxygenation improved only in 25% of patients kept in prone position, and it was not maintained in half of these after re-supination [20]. According with Coppo et al. pronation positioning is feasible and effective in rapidly improving blood oxygenation in awake patients with COVID-19-related pneumonia requiring oxygen supplementation or NIV, however the effect was maintained in only half of their patients after re-supination [21]. The difference between our results and those of Elharrar and Coppo could be explained by the fact that their studies included a greater number of patients with severe ARDS (PO_2/FiO_2 ratio < 100), perhaps in a too advanced stage to respond to this technique. Our results show that prone position can significantly decrease respiratory rate, but this effect is not maintained with re-supination: according to Ripoll-Gallardo and colleagues, although oxygenation significantly improves after pronation, no significant differences in respiratory rate were shown between initial supine position and one hour after re-supination [22]. In line with Coppo, no statistically significant differences in respiratory rate between supination and re-supination were identified [21]. In contrast, Sartini shows that this parameter improves significantly during pronation and remains stable over the three time-points [11]. We found that dyspnoea neither improves with pronation nor after resupination; to our knowledge, no published study has statistically analyzed this parameter. Furthermore, we collected baseline blood tests to assess whether there were differences between responders and not responders: in contrast to Coppo's data in which high levels of C-reactive protein and lactic dehydrogenase were positively associated with the response to pronation [21], we found no statistically significant differences. These results could be explained by the different population size of the two studies. We found a significant difference in the curve slope of PO_2/FiO_2 ratio comparing T0 and T1 in responders and non-responders: this important result shows that a lack of a substantial increase in the ratio between supine and prone position could predict a failure of the technique. Based on our experience and literature data [13-15], we recommend pronation cycles lasting at least three hours each three times a day. Prone position should be maintained as long as possible, but if poorly tolerated, temporary lateral decubitus position can be assumed. Vital signs such as saturation, blood pressure and heart rate should be monitored throughout the manoeuvre, at one-hour intervals. Considering that we did not use analgo-sedation, we decided to perform three separated cycles (one in the morning, one in the afternoon and one in the night) to allow a short break in order to increase patients cooperation. All patients included in the study tolerated pronation awake even for more than three hours and no cases of claustrophobia to helmet-CPAP were recorded; however, we believe that analgo-sedation could improve of lack of compliance to the manoeuvre, especially at night when the prone position could be maintained throughout sleep. The time limit set to establish whether pronation was effective or not depended on the starting PO_2/FiO_2 ratio value and the clinical status of patients: in case of subjects with moderate ARDS and a good respiratory rate we observed PO_2/FiO_2 ratio trend till 24-48 hours, while in those with tachypnea or severe ARDS we asked for anesthesiological consultation even in case of a lack of improvement after a single cycle. Overall, 17 (85%) patients were survivors and 3 (15%) died. All responders patients survived, while among not responders all patients died, except one; considering this, responders patients may have a better outcome, however, given the retrospective study design, the small sample size, and the lack of a control group with the same characteristics, our data are not sufficient to establish whether pronation increses survival and reduces intubation risk. Further studies are needed to confirm our results on a longer scale, also to understand whether this technique decreases overall mortality rate or it just improves gas exchange.

Conclusions

Based on our experience, in a health emergency such a global pandemic where available resources are limited, pronation should always be attempted in patients with COVID-19 pneumonia in ARDS undergoing helmet-CPAP.

By improving ventilation/perfusion ratio, this technique can allow reducing the high levels of FiO_2 and PEEP commonly used to treat this disease, thus resulting in less lung damage. We discourage from continuing with pronation when no significant increase of PO_2/FiO_2 ratio between the supine and the prone position is recorded: this could lead to treatment failure, and, in the most serious cases, to a delay of intubation.

Final considerations

- COVID-19 health emergency has led to a revaluation of prone position in non-intubated patients.
- Although some authors support that this technique improves oxygenation, for others this improvement is not maintained even after resupination.
- An important information introduced by our work is to stop pronation when no significant increase of PO_2/FiO_2 ratio between the supine and the prone position is recorded.

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