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ORIGINAL RESEARCH

Evaluation of the response to prone positioning in awake patients with COVID-19

Avaliação da resposta à posição prona em pacientes acordados com COVID-19

Evaluación de la respuesta a la posición prono en pacientes despiertos hospitalizados con COVID-19

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ABSTRACT | This study aims to evaluate the acute effects of the responses to prone positioning (PP) in awake patients with COVID-19. A prospective, single-centered study, using supplemental oxygen, was conducted with 32 awake patients with COVID-19. The response to PP was performed for 30 minutes. According to their tolerance, the patients were instructed to daily remain in PP. The variables for oxygen saturation (SpO2), heart rate, respiratory rate, ROX index and intensive care unit (ICU) admission rate were registered. In total, 25 patients (78.1%) responded to PP, with 13 (40.6%) showing persistent response and 12 (37.5%) showing transient response. Seven patients (21.9%) did not respond. Patients with persistent and transient responses increased SpO2 ($p<0.001$) and ROX index ($p=0.001$ and $p<0.001$, respectively), and reduced heart rate ($p=0.01$ and $p=0.02$, respectively), and respiratory rate ($p=0.003$ and $p=0.001$, respectively). The variables were similar in patients who did not respond to PP. The ICU admission rate of patients who had persistent or transient response, or did not respond was 30.8% (4/13), 41.7% (5/12), and 57.1% (4/7), respectively. The patients who responded to PP showed reduced heart and respiratory rates and increased ROX index, without interfering in the hospitalization rate.

Keywords | COVID-19; Coronavirus; Prone positioning; Intubation; Respiratory Therapy; Intensive Care Units.

RESUMO | O objetivo deste estudo foi avaliar os efeitos agudos dos tipos de resposta à posição prona (PP) em pacientes acordados com COVID-19. Realizou-se um estudo prospectivo, unicêntrico, com 32 pacientes acordados com COVID-19, e com uso de oxigênio suplementar. A resposta à posição prona foi feita durante 30 minutos. Após o teste, os pacientes foram orientados a permanecer na PP diariamente, de acordo com a tolerância de cada um. As variáveis saturação de oxigênio (SpO2), frequência cardíaca, frequência respiratória, índice ROX e taxa de internação na unidade de terapia intensiva (UTI) foram registradas. Um total de 25 pacientes (78,1%) responderam à PP, sendo que 13 (40,6%) apresentaram resposta persistente e 12 (37,5%) transitória. Sete pacientes (21,9%) não responderam. Os pacientes com respostas persistente e transitória tiveram aumento da SpO2 ($p<0,001$) e do índice ROX ($p=0,001$ e $p<0,001$, respectivamente), e redução das frequências cardíaca ($p=0,01$ e $p=0,02$, respectivamente) e respiratória ($p=0,003$ e $p=0,001$, respectivamente). Não houve diferença em nenhuma das variáveis nos pacientes que não responderam à PP. A taxa de internação na UTI dos pacientes que apresentaram resposta persistente, transitória ou que não responderam foi de 30,8% (4/13), 41,7% (5/12) e 57,1% (4/7), respectivamente. Conclui-se que

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os pacientes que responderam à PP apresentaram redução das frequências cardíaca e respiratória e aumento do índice ROX, sem interferir na taxa de internação.
Descritores | COVID-19; Decúbito Ventral; Intubação; Terapia Respiratória; Unidades de Terapia Intensiva.

RESUMEN | El propósito de este estudio fue evaluar los efectos agudos de los tipos de respuesta a la posición prona (PP) en los pacientes despiertos hospitalizados por COVID-19. Se realizó un estudio prospectivo, unicéntrico, con la participación de 32 pacientes hospitalizados por COVID-19 y con el uso de oxígeno suplementario. La respuesta a la posición prono se realizó durante 30 minutos. Después de la prueba, se orientó que los pacientes permanezcan en la PP diariamente según su tolerancia. Se registraron las variables saturación de oxígeno (SpO2), frecuencia cardiaca, frecuencia respiratoria, índice ROX y tasa de ingreso a la unidad de cuidados intensivos (UCI). Un total de 25 pacientes (78,1%) respondieron a la PP, de los cuales 13 (40,6%) tuvieron respuesta persistente y 12 (37,5%) presentaron respuesta transitoria. Siete pacientes (21,9%) no respondieron. Los pacientes con respuestas persistentes y transitorias presentaron un incremento de la SpO2 (p<0,001) y el índice ROX (p=0,001 y p<0,001, respectivamente), y una reducción de las frecuencias cardiaca (p=0,01 y p=0,02, respectivamente) y respiratoria (p=0,003 y p=0,001, respectivamente). No hubo diferencia en ninguna de las variables en los pacientes que no respondieron a la PP. La tasa de ingreso en la UCI de pacientes que tuvieron una respuesta persistente, transitoria o que no respondieron a la PP fue de un 30,8% (4/13), un 41,7% (5/12) y un 57,1% (4/7), respectivamente. Se concluye que los pacientes que respondieron a la PP tuvieron una reducción de las frecuencias cardiaca y respiratoria, e incremento del índice ROX, sin interferir en la tasa de hospitalización.
Palabras clave | COVID-19; Posición Prona; Intubación; Terapia Respiratoria; Unidades de Cuidados Intensivos.

INTRODUCTION

COVID-19 quickly became a global pandemic, causing problems for health systems due to the demand of mechanical ventilators, intensive care unit (ICU) beds, among other hospital supplies. Since patients who progress to invasive mechanical ventilation usually have poor results, strategies that reduce the need for intubation are required[1]. Prone positioning (PP) is a strategy employed in mechanically ventilated patients with acute respiratory distress syndrome (ARDS)[2]. PP in patients with ARDS, but without COVID-19, under mechanical ventilation can improve oxygenation and reduce mortality from 32.8% to 16% in 28 days[3,4]. The Surviving Sepsis Campaign COVID-19 Guidelines recommend PP as a therapeutic option for patients with COVID-19 and ARDS[5]. Awake patients with COVID-19 may have the same benefits on oxygenation, reducing the need for invasive ventilation[6].

The use of PP in awake patients is an adjunct method used to correct low blood oxygen, and may be associated with supplemental oxygenation, high-flow nasal cannula (HFNC) or noninvasive ventilation (NIV). Although few studies confirm PP benefits on physiological variables or intubation rate, it improves oxygenation, reduces respiratory effort and the need for intubation[7,8]. PP favors the use of alveolar units in the dorsal region, making the distribution of ventilation more homogeneous. It also relieves the compressive force of the mediastinum and the abdominal cavity in the pulmonary regions, originally dorsal[3,9]. As the dorsal region has a higher pulmonary perfusion, PP reduces the shunt, thus improving the ventilation/perfusion relation and low blood oxygen[10].

However, awake patients subjected to PP requiring supplemental oxygen may show different responses on peripheral oxygen saturation and heart and respiratory rates. Such responses may be permanent, transient, or even absent. We believe that the response to PP can interfere with physiological variables and predict the need for ICU admission. This study aimed to evaluate the acute effects of different responses to PP in awake patients with COVID-19.

METHODOLOGY

Study design

This is a prospective, single-centered study, conducted from October to December 2020, at the Hospital Sociedade Portuguesa de Beneficência de

Campos, in Campos dos Goytacazes (RJ) and at the Research Laboratory in Pneumo-functional and Intensive Physical therapy (LAPEFIPI) of the Institutos Superiores de Ensino do CENSA (ISECENSA). All patients included in the study signed a written informed consent form.

Sample

The study included 32 awake patients diagnosed with COVID-19 based on PCR tests and chest tomography with suggestive findings, spontaneously breathing and depending on supplemental oxygen. The inclusion criteria were: (1) patients aged <18 years, (2) peripheral oxygen saturation less than 92% with supplemental oxygen administration <6L/min by nasal cannula or reservoir mask; (3) not using NIV or HFNC; (4) continuous monitoring with pulse oximeter; (5) patients able to follow the instructions; and (6) tolerance to PP with minimal assistance. Patients with hemodynamic instability, severe obesity, or unable to tolerate and cooperate with PP were excluded.

To perform the PP test, patients were instructed to change from decubitus to PP, adopting the swimmer's posture for 30 minutes and maintaining previous supplemental oxygenation (device and fraction of inspired oxygen). After the test, all patients were instructed to daily remain in PP for at least six hours or more, according to their tolerance. PP was performed alone, without the use of noninvasive mechanical ventilation or HFNC. Arterial gas analysis was performed every morning before PP.

The patients with persistent response were those who had an increase of at least 5% in SpO2 during PP for 30 minutes and who maintained the increase for 15 minutes after returning to the supine position. The transient response was determined by an increase of at least 5% during PP, but not maintaining it for 15 minutes after returning to the supine position. Patients who did not respond to PP did not show increase of at least 5% during the PP or in return to the supine position.

Peripheral oxygen saturation (SpO2), respiratory rate (RR), heart rate (HR), ROX index, and ICU admission rate were evaluated according to the response during the test. The criteria for ICU admission included maintenance of SpO2 lower than 90% with oxygen flow of 15L/min, RR greater than 30 breathings per minute, reduction of the level of consciousness or clinical signs of persistent increase in ventilation as a paradoxical ventilatory pattern. The patients were only observed during their hospital stay, with the outcomes of hospital discharge or ICU admission. SpO2 and HR were measured by a portable pulse oximeter, before, 15, and 30 minutes during PP, and 5 and 15 minutes after returning to the supine position. The RR and the ROX index were registered before and 15 minutes after the procedure, both in the supine position. The RR was measured by counting the breathing cycles determined by the expansion of the rib cage by one minute, before and 15 minutes after returning to the supine position. The ROX index was calculated by the ratio between SpO2/FiO2 and the RR. Adverse events were monitored in the study.

Analysis

Initially, the data was analyzed separately. The categorical variables of the study were based on absolute and relative frequencies; and the continuous variables were based on mean and standard deviation, according to the analysis of the data distribution by the Shapiro-Wilk test.

The analysis of variance (ANOVA) was used to a factor to compare the means of the initial measurements (pre-pronation) between the groups of interest and the chi-square test for relative proportions. The tests analyzed the main results based on the normality of the sample within each group. RR and ROX index were compared using the Student t-test for repeated samples or the Wilcoxon test. The comparison between the variables analyzed in more than two times (SpO2 and HR) occurred by ANOVA for repeated samples with Sidak post-test or Friedman test, while p-value penalty for the number of combinations of two to two subgroups was performed with the Wilcoxon test. Therefore, a 0.005 significance level of the Friedman test was established. A significance level of 5% was used for all analyses.

RESULTS

We included 39 patients with COVID-19 for the study, and we excluded four for not tolerating to stay in PP during

the response test and three for not consenting to participate in the study. All 32 remaining patients tolerated PP and did not drop at least 2% in SpO2. Patients did not receive sedation or anxiolytics during the response test. The mean hospital stay was 4.6±2.7 days (2–14 days). Table 1 shows the characteristics of the patients, according to their responses.

Table 1. Sample characteristics according to the response to prone positioning

	Persistent response N=13	Transient response N=12	No reply N=7	p-value
ICU admission, N (%)	4 (30.8%)	5 (41.7%)	4 (57.1)	0.517[a]
Age (years)	55.9±14.7	58.3±8	50.5±16.8	0.990[b]
Male, N (%)	9 (69.2%)	10 (83.3%)	4 (57.1%)	
Hospital stay (days)	5.4±3.5	4.1±2.1	4±1.4	0.742[b]
SpO2 (%)	85.8±4.4	87.8±4.4	85.3±4.4	0.422[b]
HR	92.7±13.8	91.2±11.6	84.0±10.2	0.317[b]
RR	26.5±4.9	26.9±3.9	27.6±6.1	0.903[b]
ROX Index	6.7±2.7	7.6±3.1	6.8±2.3	0.520[b]
Arterial blood gas				
PaO2	61.8±11.9	64.8±6	65.9±8	0.615[b]
pH	7.46±0.05	7.45±0.03	7.44±0.04	0.716[b]
PaCO2	35.0±17.4	28.3±5.8	29.9±9.8	0.531[b]
$HCO3^-$	21.0±4.2	23.4±2.7	23.1±3.6	0.390[b]
Oxygenation				
Nasal cannula	9/13 (69.2%)	10/12 (83.3%)	6/7 (85.7%)	
Reservoir mask	4/13 (30.8%)	2/12 (16.7%)	1/7 (14.3%)	
Comorbidities, N				
Arterial Hypertension	5	3	4	
Diabetes	1	2	2	
COPD	2	1	0	
Obesity	0	0	1	

Data on measurements in the supine position prior to the procedure.

Values expressed as mean and standard deviation.

[a]: chi-square test; [b]: analysis of variance (ANOVA); COPD: chronic obstructive pulmonary disease.

In total, 25 patients (78.1%) responded to PP, with 13 (40.6%) showing persistent response and 12 (37.5%) showing transient response. A total of seven patients (21.9%) did not respond to the PP test. The ICU admission rate of patients who showed persistent, transient response, or did not respond to PP was 30.8% (4/13), 41.7% (5/12), and 57.1% (4/7), respectively.

Patients with persistent and transient response reduced SpO2 ($p<0.0001$ and $p<0.0001$, respectively), HR ($p=0.01$ and $p=0.02$, respectively), RR ($p=0.003$ and $p=0.001$, respectively), and ROX index ($p=0.001$ and $p<0.001$, respectively) after returning to the supine position, compared to pre-pronation. The variables were similar in patients who did not respond to PP. The results are shown in Table 2.

Table 2. Behavior of peripheral oxygen saturation, heart rate, respiratory rate, and ROX index, according to the response to prone positioning

	Pre	15min	30min	Post 5min	Post 15min	
	Supine	Prone		Supine		p-value
SpO2 (%)						
Persistent response	85.4±4.6	91±6	92.7±3.8	91.1±3.9	92.2±2.7	<0.0001[a]
Transient response	87.8±4.4	91.3±4	93.3±3.5	88.5±7.3	88.5±4.6	<0.0001[a]
No response	86.3±3.8	85.5±4.5	86.3±3.7	84.8±5.5	82.5±5.2	0.406[a]
HR (bpm)						
Persistent response	92.1±13.5	88±10.8	84.7±10.5	84.3±11.2	83.2±11.8	0.01[a]
Transient response	91.2±11.6	84.4±16	81.6±15	79.8±15.7	82.1±15.4	0.02[a]
No response	84±11.2	86.5±7.7	85.2±8.3	83.3±9.7	84.3±10.2	0.525[a]
RR (ripm)						
Persistent response	26.5±4.9	-	-	-	24.2±3.5	0.003[b]
Transient response	26.9±3.9	-	-	-	25.4±4.4	0.001[b]
No response	27.6±6.1	-	-	-	28.4±4.8	0,457[b]
ROX Index						
Persistent response	6.7±2.7	-	-	-	7.7±2.8	0.001[b]
Transient response	7.6±3.1	-	-	-	8.3±3.2	<0,001[b]
No response	6.8±2.3	-	-	-	6.3±1.9	0.670[b]

Values expressed as mean±standard deviation.
[a]: ANOVA for repeated samples with Sidak post-test or Friedman test; [b]: Student t test for repeated samples or Wilcoxon test.

DISCUSSION

Although the effects of PP in ARDS patients under invasive mechanical ventilation are established, the response in patients with COVID-19, especially in awake patients, lacks evidence[11]. We identified different responses to the PP test. Patients who showed permanent and transient responses (25 out of 32) increased SpO2 in the first 15 minutes of PP, which was maintained for up to 30 minutes. We observed a reduction in HR in both responses during PP and after returning to the supine position. And the response to oxygenation reduced RR and increased the ROX index. But, the absence of response did not change all analyzed variables. Out of 25 patients with permanent or transient response, nine (36%) were admitted to the ICU. Among seven patients who did not respond to PP, four (57.1%) were admitted to the ICU.

The results of a systematic review with 220 patients showed that, in 11 of the 13 analyzed studies, PP in awake patients with COVID-19 improved their oxygenation, verified by SpO2, PaO2/FiO2 relation, PaO2 or SaO2. Intubation and mortality rates were 23.8% (50/210) and 5.41% (5/203), respectively. Nasal cannula, reservoir mask, HFNC, NIV, and Helmet CPAP were used. The authors indicated subjective improvement in patients who were not intubated[12]. Taboada et al.[13] observed that SpO2 increased in 79.3% of the patients (23/29) after one hour in PP, and only 62% maintained this increase. Taboada et al. observed that 89.6% of the patients were discharged from the hospital, and only five of the 29 patients were admitted to the ICU. In our study, 78.1% of the patients responded during 30 minutes of PP and 40.6% of those were admitted to the ICU. Ng, Tay, and Ho[9] conducted a study with 10 patients on oxygen supplementation, subjected to five daily sessions of PP for one hour, with a three-hour interval. The authors observed that 30% of the patients were admitted to the ICU and only one progressed to invasive mechanical ventilation. Thompson et al.[14] observed

a heterogeneous response to SpO2 in 25 patients with oxygen supplementation, with increase between 1% and 37%. However, 48% of the patients progressed to invasive mechanical ventilation. Elharrar et al.[15] identified three types of responses based on the increase of PaO2 in PP of at least 20%, compared to the previous supine position in patients with oxygen supplementation. PaO2 increased 25% in PP, but regressed after returning to the supine position. Coppo et al.[8] conducted a study with 56 patients in PP for more than three hours, observing improvement in oxygenation, but only half kept the improvement after supination. Unlike our findings, there was no reduction in RR. Besides, the need for intubation between responders and non-responders was similar (26% and 30%, respectively).

As oxygenation generally improves with PP in an awake patient, a potential risk would delay intubation that could worsen the prognosis, as shown in previous studies conducted with patients without COVID-19. Coppo et al.[8] found no difference in intubation time between responders and non-responders in their cohort of patients with COVID-19. A multicentered cohort study conducted in 36 ICUs included 199 patients with respiratory failure due to COVID-19 treated with HFNC alone or combined with PP. The intubation rate did not reduce, having a potentially negative impact, for it was associated with late intubation. There was also no change in mortality in 28 days[11]. Evidence to support PP is limited to prospective or retrospective cohorts and case reports with small samples, which describe improvement in oxygenation during PP. However, it is uncertain the real impact of improved oxygenation on clinical results, such as mortality. Cardona et al.[16] performed a meta-analysis that evaluated the intubation rate in awake patients subjected to PP associated with supplemental oxygen or NIV. The estimated intubation rate in these patients was 30%. We understand PP as a practical and promising intervention for patients requiring supplemental oxygen or NIV, and may prevent intubation.

The clinical benefits are improvement in oxygenation, prevention of intubation, reduction of respiratory work or reduction of self-inflicted lung injury by the patient[17]. However, the prevention of intubation may be influenced by clinical decision. A recent review noted that the selected studies were heterogeneous compared to the severity of low blood oxygen. Because this is a new disease some questions remain open, such as the real effects on intubation and mortality, the form of administration regarding the frequency and duration or the identification of the patient eligible for continuity of PP[18].

The ROX index is a simple tool designed to evaluate the evolution or worsening of patients with pneumonia in order to avoid a delayed intubation[19]. The index represents a ratio of oxygen saturation, measured as the ratio between SpO2/FiO2 and RR. Its introduction when selecting patients with COVID-19 could detect early those at high risk of intubation. A retrospective multicentered observational study evaluated the selection of 273 patients with COVID-19, noting that the ROX index values showed a moderate positive correlation with the PaO2/FiO2 ratio. Thus, low ROX values were associated with low PaO2/FiO2. Besides, patients who obtained low values in the ROX index showed lower SpO2, and higher RR and intubation rate[20]. In our study, patients who responded permanently or transiently reduced their RR and increased their ROX index. Winearls et al.[21] used the ROX index to verify the clinical performance of patients with continuous positive airway pressure (CPAP), suggesting that their evaluation could be beneficial to achieve effective ventilation. Panadero et al.[22] observed that, in patients with COVID-19 under HFNC, values of the ROX index below 4.94 were associated with a higher risk of intubation. Thus, the ROX index can assist in making correct prognostic decisions.

This study has some limitations. First, the cohort size is limited to evaluate the potential of PP toward ICU admission rate. Patients also showed different patterns of permanence in PP during hospitalization. Although they tolerated the PP test, the patients remained for different periods after the test, making it impossible to quantify the daily time or total length of stay in PP during hospitalization. However, these criteria allowed this study to immediately focus on a less critical population, but associated with a high evolutionary risk, for which a specific tool would bring benefits to the entire organization. The decision to use a period of 30 minutes was taken arbitrarily, but a longer period may limit the influence of PP on the results.

CONCLUSION

Patients who responded permanently or transiently to PP showed an increase in SpO2 and ROX index,

in addition to a reduction in HR and RR. There was no difference in the ICU admission rate.

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