Analysis of the impact of pronation maneuver in patients on mechanical ventilation with diagnosis of pneumonia by Covid-19 and acute respiratory distress syndrome

Análise do impacto da manobra de pronação em pacientes em ventilação mecânica com diagnóstico de pneumonia por Covid-19 e síndrome do desconforto respiratório agudo

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ABSTRACT
Objective: To analyze the profile of patients on invasive mechanical ventilation with SARS-CoV-2 pneumonia who were pronated and who developed acute respiratory distress syndrome. Methods: Historical cohort study through the analysis of a database containing 282 patients hospitalized in a large university hospital in the city of Porto Alegre, Brazil. The population studied included individuals infected with SARS-CoV-2 and with a clinical course marked by severe pneumonia and, mainly, by acute respiratory distress syndrome, submitted to mechanical ventilation and invasive pronation maneuver. Results: Database analysis showed a high mortality rate for all patient groups and a high case fatality rate, especially in elderly patients and in individuals with active oncologic disease or with chronic kidney disease. Conclusions: The high overall mortality rate, as well as the high lethality, especially in elderly patients and in individuals with active oncologic disease or with chronic kidney disease, suggests that, for certain specific population groups, the prone maneuver is not effective in reducing high. mortality caused by acute respiratory distress syndrome associated with COVID-19.

Keywords: acute respiratory distress syndrome, pronation, COVID-19.

RESUMO
Objetivo: Analisar o perfil dos pacientes em ventilação mecânica invasiva com pneumonia SRA-CoV-2 que foram pronunciados e que desenvolveram síndrome de desconforto respiratório agudo. Métodos: Estudo de coorte histórico através da análise de um banco de dados contendo 282 pacientes internados em um grande hospital universitário na cidade de Porto Alegre, Brasil. A população estudada incluiu indivíduos infectados com SRA-CoV-2 e com um curso clínico marcado pela pneumonia grave e, principalmente, pela síndrome do desconforto respiratório agudo, submetidos à ventilação mecânica e à manobra de pronação invasiva. Resultados: A análise do banco de dados mostrou uma alta taxa de mortalidade para todos os grupos de pacientes e uma alta taxa de casos fatais, especialmente em pacientes idosos e em indivíduos com doença oncológica ativa ou com doença renal crônica. Conclusões: A alta taxa de mortalidade geral, assim como a alta letalidade, especialmente em pacientes idosos e em indivíduos com doença oncológica ativa ou com doença renal crônica, sugere que, para certos grupos populacionais específicos, a manobra de pronúncia não é eficaz para reduzir a alta mortalidade causada pela síndrome do desconforto respiratório agudo associada à COVID-19.

Palavras-chave: síndrome do desconforto respiratório agudo, pronação, COVID-19.

1 INTRODUCTION

The Coronavirus disease 2019 (COVID-19) became a pandemic declared by the World Health Organization on March 11, 2020 (1). This disease, which affects individuals of all ages, has interpersonal contact or the dispersion of droplets and aerosols in ambient air as its main forms of transmission (2).

Most patients infected with SARS-CoV-2 remain asymptomatic or have mild, nonspecific symptoms such as tiredness, myalgia, fever, cough, and a runny nose (3). Respiratory symptoms, explained by the tropism of the virus to the pulmonary epithelium,

represent the most striking features of the disease, ranging from mild symptoms to forms with severe evolution, in which tachydyspnea and respiratory failure mark the severity of the evolution (4).

Diagnosis of covid-19 can be made by detecting SARS-CoV-2 virus through nasopharyngeal swab collection using reverse transcription polymerase chain reaction (RT-PCR) assay as an ideal method (5). Computed tomography of the chest demonstrates a ground glass distribution of the condition (6).

The treatment of these patients involves only basic support measures, such as hydration, good nutrition, rest at home, use of analgesics and antipyretics, and social isolation (7).

Some patients, however, develop hypoxemia and worsening of the ventilatory pattern, requiring hospitalization and increasing oxygen support, such as non-invasive mechanical ventilation, high-flow nasal cannula, or orotracheal intubation that require invasive mechanical ventilation (8). At this critical moment of the disease, the patient is already facing the worst stage of the spread and repercussion of the virus in his lungs: acute respiratory distress syndrome (ARDS).

ARDS, whose main cause is pneumonia, is marked by severe lung injury, represents the most severe spectrum of acute lung injury, and is very common in patients admitted to intensive care beds who are undergoing invasive mechanical ventilation (9).

The main pathophysiological consequence of ARDS is the disturbance of the ventilation/perfusion ratio (V/Q), a phenomenon marked by the occurrence of intraparenchymal pulmonary shunt, that is, the presence of well-perfused but poorly oxygenated alveoli (10).

The change in position to the prone position (pronation) reduces the V/Q imbalance and the intraparenchymal pulmonary shunt that predominates in the lung bases and posterior lung (gravity-dependent regions). After performing the prone maneuver, in most cases, a rapid recovery of oximetry can be seen with an improvement in the PaO2/FiO2 ratio (10).

However, the prone maneuver is controversial in the medical literature. Despite the clear benefits in improving pulmonary oxygenation, as well as reducing intraparenchymal pulmonary shunting, studies involving this topic discuss whether this maneuver reduces mortality when applied to patients with severe rashes caused by COVID-19 or other causes (11–14)

In this context, the maneuver would have the power to temporarily improve tissue oxygenation, prolonging hospital stay, but without reducing the mortality rate in patients affected by the syndrome.

2 METHODS

This is a historical cohort study carried out through the analysis of a database of the physiotherapy service of Hospital São Lucas containing 282 patients admitted to the Emergency Department or the Intensive Care Center of this same hospital from June 30, 2020 to July 31 2021. The project was approved by the ethics committee of the university of the teaching hospital (protocol n. 53645721.4.0000.5336). Informed consent was waived due to the retrospective nature of the study.

The population studied included patients infected with Sars-Cov-2 who had a critical clinical course marked by severe pneumonia and, mainly, by ARDS.

The patients in the sample underwent treatment with a high-flow nasal cannula; however, all patients presented clinical worsening, even with high oxygen support, requiring orotracheal intubation, invasive mechanical ventilation and, therefore, were submitted to the pronation maneuver.

2.1 VARIABLES ANALYZED

The main variables analyzed were the patients' clinical comorbidities, as well as their risk behaviors. These variables include quantitative variables (age and extent of viral pneumonia) and categorical variables (race, gender, outcome - hospital discharge or death - and comorbidities presented - neurological, respiratory, cardiac, metabolic, renal and digestive). The risk behaviors included were smoking, alcohol consumption and drug use.

2.2 INCLUSION CRITERIA

The inclusion criteria for patients were: patients aged 18 years or older; patients diagnosed with COVID-19 and progressing to pneumonia and Severe ARDS undergoing invasive mechanical ventilation and the prone maneuver; patients with a PaO 2/FiO 2 ratio < 100.

2.3 EXCLUSION CRITERIA

The patient exclusion criteria were: patients younger than 18 years of age; patients diagnosed with COVID-19 pneumonia, in prone position, with progression to ARDS, but who did not require invasive mechanical ventilation; patient without chest tomography imaging tests proving the extent of viral pneumonia; intubated patients diagnosed with COVID-19 pneumonia and progressing to ARDS, but with well-defined contraindications that made it impossible to apply the pronation maneuver in these cases.

2.4 STATISTICAL ANALYSIS

Quantitative variables were described by mean and standard deviation and categorical by absolute and relative frequencies. To compare means, the t-student test for independent samples was applied. In comparing proportions, Pearson's chi-square or Fisher's exact tests were applied. In case of statistical significance and polytomous variables, analysis of adjusted residuals was performed to locate significant associations. To control for confounding factors, Poisson Regression analysis was used. The criterion for entering the variable in the multivariate model was that it had a p-value <0.20 in the bivariate analysis. The significance level adopted was 5% ($p \leq 0.05$) and the analyzes were performed using SPSS version 21.0. Results are presented as odds ratios and 95% confidence intervals. The IBM SPSS Statistics program, version 26.0 (IBM Corporation, Armonk, NY, USA) was used for the analysis.

3 RESULTS

The database of the physical therapy team at Hospital São Lucas consisted of 282 patients diagnosed with COVID-19 who developed viral pneumonia and severe ARDS. All individuals in the sample selected for statistical analysis used a high-flow nasal cannula, but due to the unfavorable clinical progression of COVID-19, worsening of hypoxemia or signs of ventilatory failure, they underwent invasive mechanical ventilation and a pronation maneuver

The sociodemographic characteristics of the patients included in the study are shown in table 01, with the majority of patients being male (55%) and Caucasian (91.5%).

The mean age of patients was 63.1 years (±13.5), and most were aged between 70 and 79 years (27%). However, the sample contains a large portion of individuals aged between 60 and 69 years (25%). The small sample of patients over 80 years of age can be justified by the treatment decision only focused on the line of care with comfort measures, with orotracheal intubation and invasive mechanical ventilation not indicated in this context.

The patients' comorbidities were analyzed and grouped into groups as described in table 01. However, some risk factors were individualized, in view of the inadequacy of grouping them into systems. In view of this decision, the analysis of these variables with the outcome for each behavior considered at risk became clearer. Among them, we found smoking, alcoholism, drug use and obesity as individual variables that are present in the analysis of the research.

All patients in the sample already had some disease or risk behavior in their past medical history.

Analyzing the data collected, we found that cardiovascular diseases represent the most prevalent comorbidity, as 181 patients (64.2%) had some heart disease or had vascular disease.

Next, metabolic diseases, represented by DM, also account for a large part of the comorbidities found in the patients included in the study, as 110 patients (39%) were diabetic. Soon after, the database shows that 49 patients (17%) had some chronic respiratory pathology. Among the individualized risk factors, overweight (BMI 25 – 29) or obesity (BMI > 29%) were detected in 62 patients (22%); smoking, in turn, was recorded in 43 cases (15.2%). These two variables represent the risk factors not grouped in systems with the highest number of cases.

The study also analyzed the extent of lung parenchyma affected by viral pneumonia in patients. The mean total ground glass area found in the lungs was 60.5% (± 20.2%) of the total lung parenchyma.

Finally, one of the most important data in the first table shows that 204 (72.3%) patients died, even with the entire line of intensive care care applied to the treatment of these patients. In this way, we perceive, through this data, the severity of this pathology after the diagnosis of Severe ARDS in patients on invasive mechanical ventilation.

Table 1. Sample characterization

Variable	**N = 282**
Age (years) - mean ± SD	63,1±13,4
Age group - n (%)	
<40 years	14 (5,0)
40 to 49 years	35 (12,4)
50 to 59 years	57 (20,2)
60 to 69 years	73 (25,9)
70 to 79 years	76 (27,0)
≥ 80 years	27 (9,6)
Sex – n (%)	
Feminine	127 (45,0)
Masculine	155 (55,0)
Race – n (%)	
White	258 (91,5)
Black	18 (6,4)
Brown	6 (2,1)
Comorbidities - n (%)	253 (89,7)
Cardiovascular	181 (64,2)
Respiratory	49 (17,4)
Kidney	34 (12,1)
Neurological	10 (3,5)
Digestive	1 (0,4)
Metabolic	110 (39,0)
Obesity	62 (22,0)
Alcoholism	5 (1,8)
Smoking	43 (15,2)
Drug addiction	2 (0,7)
Oncological	13 (4,6)
Infectious	4 (1,4)
Cirrhosis	4 (1,4)
Others	67 (23,8)
Percentage of lung affected – mean ± SD	60,5±20,2
Outcome – n (%)	
Hospital Discharge	78 (27,7)

Death	204 (72,3)

Source: Cardiovascular: SAH, HF, ischemic heart disease and cardiac arrhythmias. Metabolic: diabetes mellitus. Respiratory: asthma and COPD. Neurological: ischemic stroke, hemorrhagic stroke, dementia, Parkinson's. Digestive: gastritis, peptic ulcer. Kidneys: chronic kidney disease.

Table 02 shows the association of qualitative or quantitative variables with the outcome (hospital discharge or death). Among the sociodemographic characteristics, the statistical analysis between variables and outcome reveals that age was a very determining factor that altered the outcome among the patients in the sample. We noticed an over-mortality of patients over 60 years old. Table 02 shows that the mean age among patients who died was 67 years (±12 with $p<0.01$). The analysis reveals that among all the patients who died in the sample, 155 (75.9%) were already over 60 years of age ($p < 0.01$). The mean age of patients discharged from the hospital, in turn, was 52.9 years (±11.8 years) with $p<0.001$. Still in relation to sociodemographic characteristics, the study showed that there was no significant statistical significance between gender ($p = 0.367$) and race ($p = 0.952$) when analyzing the outcomes of the patients in the sample.

However, when we are faced with the analysis of comorbidities, the following table reveals that Chronic Kidney Disease is a pathology very associated with death, since among all patients with this comorbidity, 91% died. Another relevant data was the analysis of patients with active oncological diseases, as all patients with active oncological diseases did not survive ($p = 0.023$).

When analyzing the relative risk and the confidence interval on the qualitative and quantitative variables associated with death, we noticed that patients over 60 years of age have an increased risk of death in relation to other groups of younger patients.

Patients aged between 60 and 69 years have a relative risk of 2.57 (CI 1.28 - 5.16 with $p = 0.008$); patients between 70 and 79 years old have a relative risk of 2.91 (CI 1.44 - 5.89 with $p < 0.003$) and patients aged over 80 years have a relative risk of 2.87 (CI 1.41 - 5.84 with $p < 0.004$).

Table 2. Associations with the outcome

Variable	**Hospital discharge**	**Death**	**p**
Age (years) - mean ±SD	52,9 ± 11,8	67,0 ± 12,0	<0,001
Age group - n(%)			<0,001
<40 years	9 (11,5)*	5 (2,5)	
40 to 49 years	21 (26,9)*	14 (6,9)	
50 to 59 years	27 (34,6)*	30 (14,7)	
60 to 69 years	13 (16,7)	60 (29,4)*	
70 to 79 years	7 (9,0)	69 (33,8)*	
≥ 80 years	1 (1,3)	26 (12,7)*	
Sex – n(%)			0,367

Feminine	39 (50,0)	88 (43,1)	
Masculine	39 (50,0)	116 (56,9)	
Race – n(%)			0,952
White	71 (91,0)	187 (91,7)	
Brown	2 (2,6)	4 (2,0)	
Black	5 (6,4)	13 (6,4)	
Comorbidities – n (%)	67 (85,9)	186 (91,2)	0,277
Neurological	3 (3,8)	7 (3,4)	1,000
Respiratory	13 (16,7)	36 (17,6)	0,985
Cardiovascular	43 (55,1)	138 (67,6)	0,068
Digestive	1 (1,3)	0 (0,0)	0,277
Kidney	3 (3,8)	31 (15,2)	0,016
Metabolic	24 (30,8)	86 (42,2)	0,106
Obesity	22 (28,2)	40 (19,6)	0,162
Alcoholism	0 (0,0)	5 (2,5)	0,327
Smoking	8 (10,3)	35 (17,2)	0,209
Drug addicton	1 (1,3)	1 (0,5)	0,477
Oncological	0 (0,0)	13 (6,4)	0,023
Infectious	0 (0,0)	4 (2,0)	0,578
Cirrhosis	0 (0,0)	4 (2,0)	0,578
Outras	12 (15,4)	55 (27,0)	0,059
Percentage of lung affected – mean ±SD	61,0 ± 20,0	60,4 ±20,3	0,826

Source: *statistically significant association by residual test adjusted for 5% significance

As for the analysis of comorbidities that were most related to death, we found that kidney diseases had a relative risk of 1.18 (CI 1.01 - 1.38 with $p < 0.043$) and as well as oncological diseases that had a relative risk of 1.46 (CI 1.20 - 1.76 with $p < 0.001$).

Finally, we found a record of 32 patients (11.3%) who, while performing the pronation maneuver, suffered displacement of the orotracheal tube and 1 patient suffered facial trauma with nosebleeds as a result of the unexpected event.

Table 3. Main variables related to death in patients with COVID-19 and ARDS

Variabel	RR (IC 95%)	p
Age group		
<40 years	1,00	
40 to 49 years	1,17 (0,53 – 2,57)	0,692
50 to 59 years	1,61 (0,78 – 3,33)	0,200
60 to 69 years	2,57 (1,28 – 5,16)	0,008
70 to 79 years	2,91 (1,44 – 5,89)	0,003
≥ 80 years	2,87 (1,41 – 5,84)	0,004
Comorbidities		
Cardiovascular	0,90 (0,77 – 1,06)	0,205
Kidney	1,18 (1,01 – 1,38)	0,043
Metabolic	0,96 (0,83 – 1,10)	0,554
Obesity	1,13 (0,93 – 1,36)	0,214
Oncological	1,46 (1,20 – 1,76)	<0,001
Others	1,13 (0,99 – 1,29)	0,062

4 DISCUSSION

ARDS represents the leading cause of death in patients with COVID-19 (15). The most recent studies on ARDS state that this syndrome, as a consequence of infection by Sars-Cov-2,

has a higher mortality than as a result of other pathologies (16). Hospital mortality from ARDS in patients undergoing invasive mechanical ventilation can reach 94% (16).

Published works on this topic present limitations and divergences in results and conclusions. Certainly, one of the reasons that makes it difficult to compare the studies results from the fact that each service in intensive care determines its own protocols for invasive mechanical ventilation, as well as the limits for performing the pronation maneuver. In addition, the complexity of managing these patients, as well as the emergency recruitment of physicians with no experience in critical care to work with critically ill patients, can also be a limiting factor.

It is known that the execution of the pronation maneuver brings the benefit of improving tissue oxygenation instantly after its application (17). In the sample of patients in the database, soon after placing them in the prone position, we quickly noticed an improvement in oximetry, as well as in the PaO2/FiO2 ratio. The ideal pronation time for the patient to remain in the prone position, through which there is a good improvement in tissue oxygenation, is 16 hours of permanence in this position (18). Our study was based on keeping patients in the prone position for the same period of time.

Studies that analyzed the comparison of groups of patients who remained in the supine position with patients who were prone differ among themselves on the relevance of prone position as a determining factor for reducing mortality. Guerin and colleagues showed the importance of prone when applied to patients with severe ARDS even before the 'COVID-19 era', showing an increase in survival at 28 days, as well as at 90 days for individuals submitted to prone position in relation to patients who remained for the entire hospitalization in the supine position (19). Still, Shelhamer concluded in his study that patient pronation can reduce the mortality rate by up to 40%, when applied to patients undergoing invasive mechanical ventilation for severe ARDS by Sars-cov-2, in relation to patients with the same evolution. who remained in the supine position throughout the entire hospital stay (20). In this work, however, we noticed in its sample that most patients were of African descent, unlike the other studies analyzed. On the other hand, Estenssoro, through the SATICOVID study, concluded, after randomizing patients into the prone and supine groups, that even with the application of the pronation maneuver, mortality was high in both groups; however, the group of prone patients had a higher number of deaths (19).

Despite these divergences, studies have already shown that there are controversies in the execution of the pronation maneuver as a mortality reduction factor in patients with clinical characteristics very similar to those of our sample (8, 10, 11, 20). Furthermore, there is evidence

that, in general, there is a poor evolution predominantly in male, elderly and Caucasian patients, and these individuals are rarely healthy (17-19, 21, 22). In our sample, we noticed that the majority of patients were male, Caucasian, with a mean age of over 60 years. In addition, given so many variables analyzed and correlated with the outcomes (death x hospital discharge), we found that advanced age, active oncological disease and chronic kidney disease were the comorbidities with the highest lethality, even with all support lines. and treatment for critically ill patients, including the prone group. Therefore, the reviewed studies contain samples with patients with ages, characteristics and comorbidities similar to those found in our study.

Finally, studies reveal that there is a relationship between the extension of the ground-glass area with a greater chance of death (23). The tomographic factors most associated with death, in addition to the extension of the viral pneumonia, are the reticular opacities that determine interstitiopathy and the presence of consolidations (23). In our study, however, there was no major discrepancy between the areas of extent of pulmonary involvement and the outcomes of death and hospital discharge.

5 CONCLUSIONS

Therefore, it is undeniable that there is improvement in oximetry with the prone maneuver; however, the use of different parameters on the assessment of patients makes it difficult to interpret the results when analyzing the outcomes. Still, only for younger patients, especially individuals under 60 years of age, do we realize the importance of the maneuver in reducing the number of deaths. Therefore, we must consider that, in the face of circumstances such as advanced age or some specific comorbidities, the use of this maneuver seems to be ineffective, given the high mortality in the aforementioned groups in this study.

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