

Research Article

Alveolar-Arterial Oxygen Gradient Ratio (GAaO₂) As A Predictor of Early Mechanical Ventilation In A Patient with Suspected Sars Cov-2 Infection in the Adult Continuous Admission Area of The "Dr. Gaudencio González Garza" Of The La Raza National Medical Center.

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Received: 28 August, 2023

Accepted: 29 September, 2023

Published: 04 October 2023

Abstract:

Background: Viruses and mainly COVID and the pneumonia it causes are among the pathologies that cause the greatest damage to the alveolus-capillary membrane of the lungs in patients with this disease.

Objectives: To relate the alveolar arterial oxygen gradient (GAaO₂) and the start of early mechanical ventilation in patients with SARS COV - 2 virus infection in the continuous admission area.

Methodology: Descriptive, retrospective, observational, cross-sectional, with 165 clinical records of patients admitted to the emergency area in a period from April 2020 to 2021. Kolmogorov – Smirnov test, Mann-Whitney U and Pearson correlation coefficient were performed. with $p > 0.05$, ROC curve for sensitivity and specificity with Youden index and multivariable regression analysis for correlation.

Results: A cut-off point of GAaO₂ = 210.25 was obtained with sensitivity of 95% and specificity of 94%, with 2 times more risk of starting mechanical ventilation and correlation of 89%.

Conclusion: It was observed that the cut-off point was related to greater risk and correlation of initiation of mechanical ventilation. This is a reliable value to decide the start of invasive ventilation.

Keywords: SARS COV-2, arterial blood gas analysis, alveolar arterial oxygen gradient, mechanical ventilation, comorbidities.

Introduction

In the last decade in our country, the demand for medical services has increased, more specifically in the emergency area, where, as is known, the first medical attention, evaluations and decisions are given for the management and adequate treatment of patients infected with the SARS-COV2 virus, which makes it essential that the professional in charge of this area; the emergency doctor; have elements and tools for a correct, timely and rapid diagnosis of patients who request your attention and with this provide a treatment focused on improving their prognosis.

In recent years, more specifically since 2020, let us remember that a pandemic originated with patients who developed severe

pneumonia, at that time unknown in terms of the pathophysiological mechanism, this resulted in the high mortality of these patients, which made the population In general, you will seek prompt, high-quality medical care to reduce the inherent risk of death.

According to the evolution and acquisition of medical knowledge, the multiple pathophysiological processes of the disease were known, beginning to evaluate certain aspects that increased or decreased mortality, all of this during the course of the pandemic.

Changes In The Partial Pressure Of Oxygen

The partial pressure of oxygen (PaO₂) in air is dependent on atmospheric pressure, its concentration (0.21%) is constant.

When inspiration occurs, air enters the upper airway. This anatomical structure fulfills the functions of cleaning, heating and humidifying inspired gases, which is why an acute vapor of 47 mmHg is normally found at a normal temperature.

The first drop in the partial pressure of oxygen occurs when oxygen is displaced from the gas mixture of the upper airway; the inspired pressure of oxygen (PiO_2) is calculated (1).

$$1-PiO_2 = (\text{Atmospheric pressure} - \text{Acute vapor pressure}) \times (FIO_2)$$

The second drop in the partial pressure of oxygen, the oxygen pressure does not experience any variation during its journey towards the alveolus. However, upon reaching the alveolus, a different gas appears in the mixture of carbon dioxide (CO_2), which is normally leaving the capillary to be eliminated in the expiratory phase. This gas exerts pressure and determines the

alveolar oxygen pressure (PAO_2) which is calculated using the following formula.

$$2-PAO_2 = PiO_2 - PaCO_2/0.8$$

The third drop in the partial pressure of oxygen establishes a gradient or arterial alveolus oxygen difference $GAAO_2$ which has a value between 5 to 10 mmHg when breathing with an FIO_2 of 21%.

$$3-GAAO_2 = PAO_2 - PaO_2$$

Physiologically, the upper limit of $GAAO_2$ is 10mmHg. In critically ill patients, values of up to 15mmHg in young adults and up to 38mmHg in the elderly are considered normal. A greater increase in this level should draw our attention and determine if the patient is suffering from some lung pathology (2).6

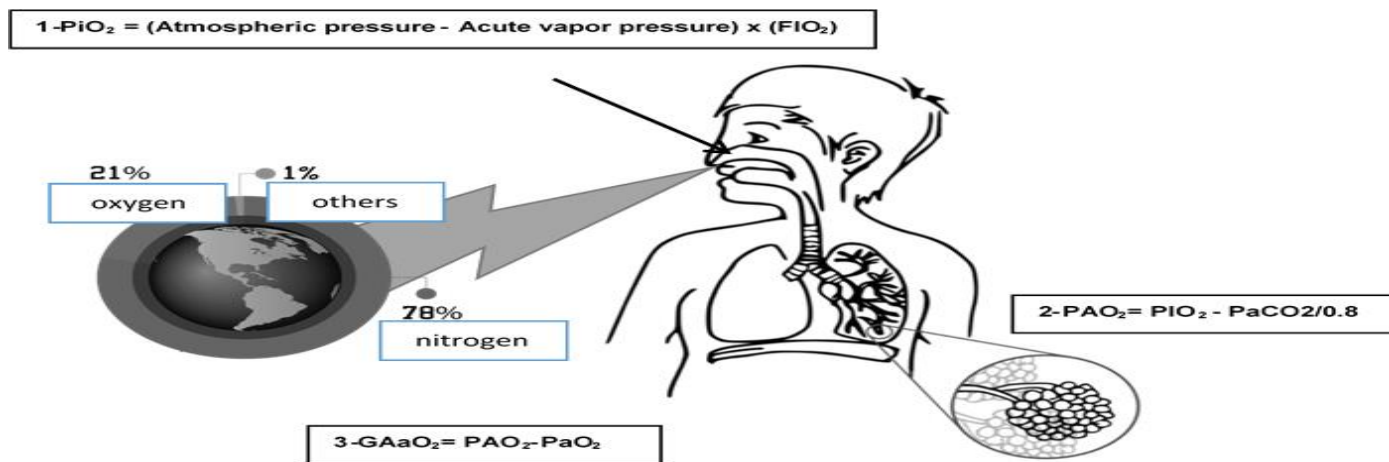


Figure 1. Modifications in the partial pressure of oxygen.

PiO_2 =Inspiratory oxygen pressure

PAO_2 =Alveolar oxygen pressure

$GAAO_2$ =Alveolar-arterial oxygen difference

Objective

The main objective of this research was to determine the association of early mechanical ventilation with one of the most important determinants of oxygen diffusion in the lung parenchyma: The alveolus-arterial oxygen gradient; remembering that, it was observed in various studies that the death of patients with infection with this virus and therefore severe pneumonia associated with respiratory failure decreased when the guideline was taken to include the patient in an invasive device that would provide oxygen early (3).

These aspects generated in the Mexican health system a decrease in costs associated with the care of patients in critical condition, according to one of the main insurance associations in this country, the approximate cost of care for a patient with severe pneumonia secondary to SARS infection. COV-2

corresponded to \$429,615.00 pesos, this taken from the IMSS tabulators (46), and they report that private institutions increased this cost to approximately \$4,000,000.00 pesos, which was seen in the medium and long term, a decrease in those costs generated and that would be billed to the budget assigned to mainly public institutions (4).

All this made us think and observe, with the resources we had, whether in the emergency department there was a quantitative parameter to evaluate lung damage early and practically and the need in patients to subject them early to invasive mechanical ventilation and thus reduce mortality rates and therefore medical care costs in a health system that, as we know, is limited and generally precarious, to which we realized that the alveolar arterial oxygen gradient was the best quantitative parameter that we had at our disposal .

This research will provide tools not only to emergency physicians, but also to doctors from other areas, since it will provide information on how these patients have behaved, which will help us provide better treatments associated with mechanical ventilation and, above all, to reduce mortality in our patients, remembering that up to this point aspects such as the alveolar-arterial oxygen gradient and its impact on the decision to initiate oxygen delivery through invasive devices have not been evaluated, according to the degree of lung damage present in the patient. .

Material and Methods

This research is retrospective, observational, descriptive, cross-

sectional. The period corresponded from April 2020 to April 2021, the collection was carried out and achieved in 2 months, we have a population of 1000 patients with medical care provided in the continuous admission service for 1 year, with a confidence level of 95% and margin of error of 7%, obtaining a total of 165 patients as a sample, of which a review of the clinical record was carried out.

The numerical or quantitative variables were expressed or had as a measure of average association and parameters such as the standard deviation for data that had a normal distribution; and for those who had free distribution of use median and interquartile range (IQR). A normality test was applied that was obtained through the Kolmogorov-Smirnov test. These categorical variables obtained were expressed in number of observations (n) and percentages (%). We compared the clinical and demographic variables, and used the Student t test for numerical variables that had a normal distribution, and the Mann-Whitney U test for those that had a non-parametric distribution.

We used the Chi square test. Subsequently, an ROC curve was performed for sensitivity and specificity guided by the cut-off point according to the Youden index. We used a multivariate regression analysis to specify this association. Finally we obtained a statistically significant value, a value of $p < 0.05$. We used a statistical package SPSS IBM version 25.

Results

165 patients with COVID-19 were analyzed in the adult continuous admission area, the median age was 59 years (range 51.5-66), the male sex was 104 patients (61.5%), the median with personal pathological history was 5 (range 4-9), the mean of atmospheric pressure 585 (.078), median PaO₂= 45 (range 39-54), median paCO₂= 29 (range 24-35), median FiO₂ was 35 (range 30-40), median SaO₂ 81 (65-87), median GAaO₂ pre mechanical ventilation was 238 (range 227.6-252.6), mean PaO₂ pre mechanical ventilation 45.8 (SD 13), mean PaCO₂ 33.2 (SD 7.9), AVM 59 (34.9%), AVM admission 24 (14.2%), more details in the following table 1 where relevant aspects of the population are described.

Table 1. Baseline characteristics of the population.

Characteristic	n=165
Sex, n (%), Male	104 (61.5%)
Age, median (IQR), years	59 (51.5-66)
APP, median (IQR), number of antecedents	5 (4-9)
Atmospheric pressure, mean (SD)	585 (.078)
PaO ₂ , median (IQR)	45 (39-54)
paCO ₂ , mean (IQR)	29 (24-35)
FiO ₂ , median (IQR)	35 (30-40)
SaO ₂ , median (IQR)	81 (65-87)
GAaO ₂ Baseline, median (IQR)	109.6 (68.4-147.5)
PaO ₂ pre mechanical ventilation, median (SD)	45.8 (13)
PaCO ₂ pre mechanical ventilation, median (SD)	33.2 (7.9)
FiO ₂ pre mechanical ventilation, median (SD)	60 (5.1)
SaO ₂ , median (IQR)	65 (56-73)
GAaO ₂ pre mechanical ventilation, median (IQR)	238 (227.6-252.6)
AVM, n (%)	
yes	59 (34.9)
no	106 (97.6)
AVM income, n (%)	
si	24 (14.2)
no	141 (97.6)

Abbreviations: IQR (interquartile range), SD (standard deviation), num (number), GAaO₂ (alveolar arterial oxygen gradient), MV (mechanical ventilation), SO₂ (oxygen saturation), PaCO₂ (carbon dioxide pressure), FiO₂ (fraction inspired oxygen).

Subsequently, the population with mechanical ventilation was divided, Table 2, and without mechanical ventilation, Table 3. Table 2, describes a bivariate analysis, between GAaO₂ pre with patients undergoing mechanical ventilation, with the median PaCO₂ pre being 29 (Range 24 -35), and in the bivariate analysis, that is, comparing one variable with another, it was 59 (33.5%), giving a p .013 with significance; the same for the mean FiO₂ 60 (SD 7.2), GAaO₂ pre 51 (30.9%), p .047; median SaO₂ pre 81 (range 65-87), for GAaO₂ pre 59 (33.5%), p .041.

Table 2. Bivariate analysis between GAaO₂ before with mechanical ventilation.

CHARACTERISTICS	n=59	GAa pre (%)	p
PaCO ₂ pre, median (IQR)	29 (24-35)	59 (33.5)	.013
FiO ₂ pre, mean (SD)	60 (7.2)	51 (30.9)	.047
SaO ₂ pre, median (IQR)	81 (65-87)	59 (33.5)	.041

Abbreviations: IQR (interquartile range), SD (standard deviation), GAa (alveolar arterial oxygen gradient), SO₂ (oxygen saturation), PaCO₂ (carbon dioxide pressure).

Subsequently, the ROC Curve (acronym for Receiver Operating Characteristic) was carried out, using it to know the cut-off point with the best sensitivity, also with the necessary specificity for this population, the study variable was GAaO₂ pre, finding a AUC (area under the curve) of .711 (described in graph 1), being greater than .50 with a p 0.006, (95% confidence interval .578-.844), for a cut-off point of 210.25 and determining a sensitivity of .958 and specificity of .944, chosen by the Youden index formula of .902, described in detail in table 4.

Figure 1 COR curve

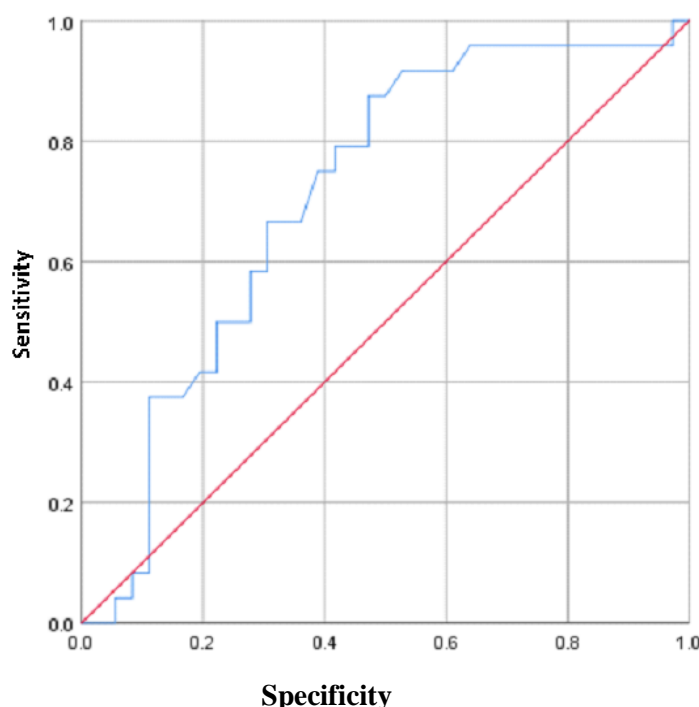


Table 3. Cut-of point for GAaO₂ by Youden index.

AUC	Cut off	Sensitivity	Specificity	95% IC	p
.711	210.25	.958	.944	.578-.844	.006

Finally, once the cut-off point was obtained, a multivariate analysis was performed to determine the association between GAaO₂ pre and mechanical ventilation; however, due to significance, an adjusted analysis was performed with the other variables, demonstrating that GAaO₂ pre>210 has an OR 2.0, (95% CI 1.33-2.73, p .021), SaO₂ pre has an OR 1.3, (95% 1.07-2.32, p .011); PaCO₂ pre obtained an OR 1.71 (95% CI 1.74-3.17, p .001), finding an association of GAaO₂ pre with mechanical ventilation adjusted to a regression model R² .089, which we observe in detail in Table 5.

Table 4. Regression analysis to predict pre GAaO₂ as a predictor of mechanical ventilation, omnibus p <0.001, R² 0.892

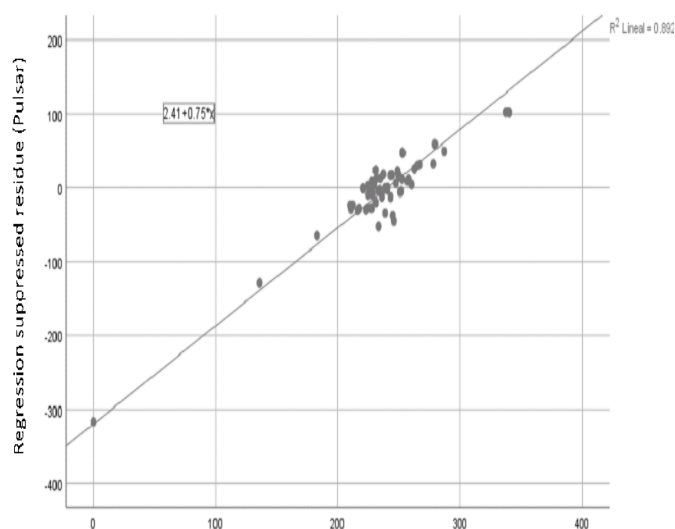
	OR	95% IC	P
GAaO ₂ pre mechanical ventilation	2.0	1.33-2.73	.021
SO ₂ pre	1.3	1.07-2.32	.011
pCO ₂ pre	1.71	1.74-3.17	.001

Abbreviations: GAaO₂ (alveolar arterial oxygen gradient), MV (mechanical ventilation), OR (odds ratio), 95% CI (95% confidence interval). SO₂ (oxygen saturation), pCO₂ (carbon dioxide pressure).

Finally, Scatter Graph 2 was obtained, where the relationship between one variable and its value increases as the other increases, obtaining a positive correlation, reflected in the cloud of points forming the data of both variables, which explains or suggests a positive linear association.

Graph 2. Scatter figure or scatter diagram, between GAaO₂ with early mechanical ventilation, R² 0.89 (89%)

**Scatter plot
GAaO₂**



GAaO₂:

In this scatter graph 2, of association between one variable and another, explaining that a low correlation coefficient is <.4

(40%), .4-.7 (40-70) is moderate correlation, and >.7 or (70%) is a strong or good correlation, which is what is sought in medicine. In this study, an adjusted R² or .89 (89%) was obtained, explaining a strong or good association between the two variables.

Discussion

The study of the alveolar arterial oxygen gradient in patients with COVID virus infection has been little applied, in this context it is necessary to observe its application and evaluation in this type of patients. The design implemented in this thesis allowed us to observe the variability of this value, both in patients who received oxygen through invasive devices, and in those who opted for a low-flow device, which helped us identify the alteration in the first instance. in the propagation of oxygen through the membrane, finding that in patients with values greater than 210.25mmHg of alveolar arterial oxygen gradient as a cut-off point in our study, they merited administration of oxygen through invasive mechanical ventilation.

Jessica González et. Al in Spain, in a report of an investigation that was carried out in 205 patients of which 140 underwent early mechanical ventilation of which 34 patients died, comparing the 65 patients in the late mechanical ventilation group of which 33 patients died, with higher mortality in those undergoing late mechanical ventilation (50.8%) compared to those undergoing early mechanical ventilation (24.3%). They also associated it with the risk of mortality in these two groups with a higher percentage in patients with late initiation of invasive ventilation (>48 hours) (5). They also observed the intubation time in patients with late mechanical ventilation, started after 3 days, to which they observed that many of the patients on day 2 presented greater deterioration and mortality increased significantly, which conditioned it to be started on that day. mechanical ventilation, determining that for each day of delay in ventilation, the risk of death increased by 3% (6).

In a research published in the Critical Care Magazine with the J-RECOVERED database where early intubation and its mortality were compared, 562 patients who met the basic criteria of the document and applied in a database were studied on that occasion. with a total of 4700 patients, of these only 412 entered into this data analysis, the age of these patients was evaluated above all and a relationship of the PaO₂ value of the patients intubated late was similar to that of the patients that warranted early intubation, this associated according to their bibliographic reviews with the presence of severe lung injury (7). They observed that the use of oxygen influenced the presentation of lung injury and subsequent staging of the disease, which they associated with the use of mechanical ventilation and it was seen that they required fewer days with this supply of oxygen at positive pressure and consequently a decrease. of hospitalization days, associating them with PaO₂/FiO₂(48).

Therefore, although oxygen diffusion in this alveolocapillary membrane has not been specifically determined in this study, these two previous indices studied in that report were available, indicating that there is alveolar dysfunction to a greater or lesser extent according to the result obtained from each index. in each patient, indirectly giving us an overview of the behavior of

oxygen and its pressures in these patients.

There is an article published in June 2022 in Research Gate in Infectious Disease Reports that focuses on the role of the alveolar-arterial oxygen gradient as an early marker to determine severe pneumonia. They found that this gradient encompasses all the important aspects of lung damage induced by this virus, in which they observed that they increased in the presence of lung damage (8). This study also compared the use of PaO₂/FiO₂ with the alveolar-arterial oxygen gradient, finding that this gradient is more specific to predict severe pneumonia, finding a value of >60mmHg as a cut-off point to determine patients who have a high probability of presenting severe pneumonia (9).

With respect to the main hypothesis, we can point out that, based on our study, chronic degenerative diseases play a determining role, especially in how this alveolar arterial oxygen gradient behaves, finding a greater association in obese patients and those with Diabetes Mellitus, the which corresponded to 10 patients, of which 4 patients underwent mechanical ventilation since their admission, finding gradients above our cut-off point of 210.25 mmHg.

Among the multiple bibliographies that talk about this gradient, we find that it has only been observed in patients with COPD, who have high limit values of 30mmHg, so we can affirm that the dysfunction of the alveolocapillary membrane in patients with SARS-COV2 presents greater dysfunction, as well as we can associate it with the patient's comorbidities, a fact that has not been evident in patients with COPD.

This research could be compared with patients with other pathologies, it is because to date this gradient has not been studied with the specific characteristics such as comorbidities, gender and age, which we are looking for. This makes us look for alternatives within the updated bibliography, where we found a thesis in Veracruz where the association of the alveolar arterial oxygen gradient with mortality in these patients was studied. They found that the higher the gradient, the greater the patient's mortality, thus We can relate its results to respiratory dysfunction. This helps us confirm in our patients that the greater the diffusion alteration, the worse the prognosis, not only for ventilation, but also for mortality and morbidity (10).

We found that the alveolar arterial oxygen gradient can be used as a predictor for a patient to undergo oxygen placement through an invasive device, since the data obtained clearly supports the hypothesis where a significant increase in the alveolar arterial oxygen gradient is observed. with respect to patients without any pathology, since in the context of alveolar-arterial gradient it has only been studied and determined in patients with COPD or chronic lung disease.

From the data obtained we can determine several aspects, initially we conclude that we can associate pathologies with the prognosis especially in the medium and short term of our patients, even with their age serious illness was associated in patients between 50 and 60 years old, all of this, as a set of data, aspects of the patients, it can be concluded that our hypothesis was corroborated, where we found that the greater the alveolar arterial oxygen gradient, the greater the requirement for supplemental oxygen, choosing invasive mechanical

ventilation.

Conclusions

The present study gives general conclusions that the alveolar arterial oxygen gradient, a cut-off point of GAaO₂ = 210.25 was obtained with sensitivity of 95% and specificity of 94%, with 2 times more risk of starting mechanical ventilation and correlation of 89 % With which we can give way to more complex management in our patients and therefore the decrease in mortality and days of stay, therefore the main objective was met in which it corresponds to the relationship that was found between this gradient and the onset of oxygen provision by an invasive device in this case mechanical ventilation and mainly early.

Thanks

None

Conflict of Interests


The authors declare no conflict of interest.

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