Original Article :

Assessment of the variation of the pulmonary gas exchange model in the critical care setting.

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Abstract

Background and Aims:

In intensive care units (ICUs), clinicians use various mathematical models to assess and monitor respiratory illness. However, evidence suggests that some pulmonary internal and external physiological factors are not integrated in the calculation of these models. This research aimed to demonstrate the variation in these models within a short period in critical care settings.

Methods:

A retrospective cohort study was conducted from 2017 to 2019 with adults admitted to an ICU and mechanically ventilated for more than 24 hours. Two different arterial blood gas samples were selected within a mean of 120 minutes. The coefficient of variation percent [(CV%)=SD/Mean] was calculated.

Results:

In total, 211 intubated ICU patients were included. The mean age was 57 (SD +/- 19.62) years, and 33% were female. The degree of variation of the average CV% for all the mathematical models was 14%-30%. The mean CV% for the arterial oxygen tension to inspired oxygen fraction (PaO2/FiO2) and arterial/alveolar oxygen tension ratio (PaO2/ PAO2) was 14%, which is a low variation compared to the respiratory index (RI) for which the mean CV% was 30%.

Conclusions:

The findings of this study indicate that most of the existing oxygen mathematical models used in clinical settings lack physiological realism, necessitating a new mathematical model that integrate both assess illness severity and enhance other models' accuracy.

Keywords:

Mathematical model - Pulmonary oxygen indices - Respiratory index - Oxygen index - Oxygen saturation index.

Introduction

Respiratory monitoring plays a significant role in critical care settings, specifically with respiratory illness. Several respiratory monitoring techniques are available, including non-invasive techniques, such as peripheral capillary oxygen saturation and invasive methods such as arterial oxygen saturation. The appropriate use of these techniques can support the understanding of respiratory illness in critical care settings.

A growing body of literature recognizes the importance of using mathematical models in the medical field.[1–5] In critical care settings, clinicians use various mathematical models to assess the cardiopulmonary status, evaluate the severity of lung damage[5–8], and monitor the oxygenation status. The components of the mathematical model equations are obtained from arterial blood gas (ABG) readings and mechanical ventilation (MV) parameters. The non-invasive nature of these mathematical models supports their wide utilization in critical care settings.[9] The models also define the nature of the impairment with some level of accuracy to indicate the appropriate management plan of patients.[10,11]

There are widely adopted mathematical models that assess the oxygen status in the critical care setting,[1,2,12,13] including the ratio of the arterial oxygen tension to the inspired oxygen fraction (PaO2/FiO2 ratio), arterial/alveolar oxygen tension ratio (PaO2/PAO2), alveolar-arterial oxygen tension difference P(A-a)O2, respiratory index (RI= (PA-aO2)/PaO2), oxygen saturation index (OSI = MAP × FiO2 × 100 /SpO2), and oxygen index (OI = FiO2 x MAP x PaO2/100). The mathematical models provide insight in the status of the lung. The measured variables, such as the atrial oxygen saturation (%SaO2) and arterial oxygen tension (PaO2), reflect the oxygen impairment. However, these values depend on various physiological factors, including internal and external factors. Internal factors include the values resulting from the non-linear nature of the relationship between PaO2 and Hb saturation in the oxygen dissociation curve, changing blood flow, and the blood acid-base balance.[1,14] However, the external factors indirectly contribute to the MV gas exchange, including the minute ventilation, respiratory rate (RR), inspiratory time, or inspiratory to expiratory ratio, total positive end respiratory pressure (PEEPt), and oxygen consumption. [14] The PaO2 alone is unreliable indicator to reflect the actual oxygenation due to their poor correlation with changes in clinical circumstances.[15,16]

In addition, some external pulmonary factors that affects oxygenation are not

included in the calculation of the mathematical models, and they less likely to accurately reflect the lung condition.[1,2,4,14] For example, Nirmalan et al examen some pulmonary oxygen indices (mathematical models) that are utilized in ICU with a simulated ARDS lung, and exemplify a degree of variation on mathematical models affected by various extrapulmonary factors.[4,14] Kathirgamanathan et al conclude that the mathematical models did not account for extrapulmonary factors when . Clinical studies reported the need for a suitable model that can adequately consider the effect of factors independent of the pulmonary configuration. This study aimed to quantify the variation of currently used mathematical models of pulmonary gas exchange (PaO2/FiO2 , (PaO2/PAO2),P(A-a)O2, RI, OSI, and OI taking in consideration the physiological factors to present a reliable indicator of the lung status during a short period, without a substantial variation within the same patient.

Methods

Study design and setting

A retrospective cohort study was conducted in critical care settings King Abdulaziz Medical City (KAMC) in Riyadh, Saudi Arabia from January 2017 - January 2019. KAMC is a 1501-bed tertiary care center and accredited by the Joint Commission International. Adult patients (>18 years), admitted to ICU and placed on MV for more than 24 hours were included irrespective of the cause of the ICU admission. We excluded patients admitted in the ICU for less than 24 hours, transferred to other hospitals, or had incomplete medical records.

Study Variables and outcome

Data were collected from the electronic medical file system for each patient. The data included demographic information (age and gender), time and results of the arterial blood gas (ABG), and the corresponding oxygen saturation at the time of arterial blood sampling. The measurements were grouped in the first and second ABG and MV parameter reading. Two consecutive ABG samples were selected within a mean period of 120 minutes, based on patient-specific needs for one day, referred to as a short period in this study. The blood samples were analyzed immediately at body temperature for pH, PaCO2 (mmHg), PaO2 mm Hg, HCO3- (mEq/L), BE (mEq/L), and Hb (g/dl). All the blood samples were obtained the same way and analyzed with the same Omni Roche® system (Roche Healthcare Diagnostics Inc., Germany). The blood gas analyzer is fully automated and it runs a quality control (QC) with prefilled cartridge solutions. Every

30 minutes, a 1-point system calibration was done and an entire system calibration every eight hours.

The following mechanical ventilator parameters were recorded the time when the ABG sample was obtained, which included the tidal volume (ml), respiratory rate (bpm), minute ventilation (L/min), peak pressure (cmH2O), PEEP (cmH2O), mean airway pressure (cmH2O), inspiratory time (sec), I: E Ratio, airflow (L/min), and FiO2. Other variables, such as length of MV use in days, were also collected. The results of the ABG and MV parameters were used to calculate the following mathematical models: PaO2/FiO2 ratio, P(A-a)O2, PaO2/PAO2, RI=(PA-aO2)/PaO2, OSI=MAP × FiO2 × 100 /SpO2, and OI=FiO2 x MAP x PaO2/100.

Statistical analysis

The patient's demographic and clinical data are presented as mean and standard deviation (SD) for the continuous variables if normally distributed, or else the median and interquartile range (IQR) were used. The categorical variables are presented as frequency and percentage. A paired t-test was used to determine whether there was a statistically significant mean difference between the parameters of MV, ABG reading, and mathematical models in the first reading compared to the second reading. The coefficient of variation percent [(CV%) = SD/Mean] was calculated to compare the scatter of variation for each mathematical model expressed in different units. All the statistical analyses were performed using a standard software package (Stata, version. 12.0; StataCorp).

The results of the study are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. The King Abdullah International Medical Center Institutional Review Board approved this study with a waiver of informed consent (Institutional Review Board approval was obtained IRB: SP20089R).

Results:

Study population

In total, 211 intubated ICU patients were included in the study. The mean age of the sample was 57±19.62 years, and 33% were female. The median length of stay (LOS) in the ICU was 15 days (IQR 6-27 days), and the median intubation duration 4 days (IQR 2-10 days). The majority (93%) of intubated patients were placed on pressure-regulated volume control (VC+ or PRVC) as the mode of ventilation. Table 1 shows the description of the MV parameters, ABG, and mathematical models for the first and second reading. For the MV settings, the mean respiratory rate in the first reading

was lower than the second reading (t(210) -3.95, p = 0.001). This was similar for the inspiratory time (t(210) -3.95, p = 0.001, and FiO2 , t(210)= 10.29, p = 0.001).

Table 1 The mean of the two-reading form Mechanical ventilation, ABG and mathematical model

Mechanical ventilator settings	1st reading mean±(SD)	2nd reading mean±(SD)	P-value
Tidal volume (ml)	406±(54.47)	408±(60.39)	0.505
Respiratory rate (bpm)	21±(3.79)	22±(4.55)	<0.001
Minute ventilation (L/min)	9.50±(2.55)	9.55±(2.51)	0.438
P peak (cmH_2O)	23±(6.70)	22±(6.66)	0.138
PEEP (cmH_2O)	7 ±(2.48)	7±(3.67)	0.319
Mean airway pressure (cmH_2O)	12 ±(3.49)	12.21±(4.19)	0.498
Inspiratory time (sec)	0.88±(0.10)	0.90±(0.14)	<0.001
I:E Ratio	1:2.13±(0.64)	1:2.25±(1.23)	0.018
Flow (L/min)	50.29±(10.92)	50.40±(10.01)	0.138
FiO_2	0.58±(0.26)	0.47±(0.19)	<0.001
ABG reading			
pH	7.33±(0.10)	7.35±(0.08)	<0.001
PaO_2 (mmHg)	132.59±(81.94)	106.14±(9.69)	<0.001
PAO_2 (mmHg)	362±(179)	284±(136)	<0.001
$PaCO_2$ (mmHg)	42.82±(10.76)	39.88±(9.69)	<0.001
HCO_3 (mmol/L)	22.20±(4.78)	22.18±(5.10)	0.842
Hb (g/dL)	10.32±(2.11)	10.61±(2.07)	0.823
Hct (%)	31.54±(6.61)	32.28±(7.81)	0.693
SaO_2 (%)	96.12±(7.49)	96.39±(9.62)	0.366
BE (mmol/L)	-2.34±(6.35)	-2.70±(6.40)	0.865
Mathematical models			
PaO_2/FiO_2 ratio	255±(137)	257±(115)	0.772
$P(A\text{-}a)O_2$	235±(172)	182±(138)	<0.001
PaO_2/PAO_2	42±(23)	44±(21)	0.176
RI	2.51±(2.62)	2.08±(2.06)	<0.001
OSI	7.64 ±(5.49)	6.15±(4.62)	<0.001
OI	7 ±(6.64)	6±(6.19)	0.012

There were statistically significant differences in the ABG reading, the mean pH, PaO2, PAO2, and HCO3 between the first and second reading. For the mathematical models, the mean P(A-a)O2 (235±172) was higher in the first reading than the mean of the second reading (182±(12=38)), with a statistically significant increase of 53.18 (95%CI 39.62-66.76), t(205)=7.71, p=0.001). For the RI, the mean was higher in the first reading (2.25±2.62) than the second reading (2.08±2.06) with a statistically significant increase of 0.44, 95%CI 0.21-0.66),t(205)=3.77, p=0.002). For the OSI, the mean was also higher in the first reading (7.64± 5.49) than the second reading (6.15±4.62), with a statistically significant increase of 1.49, 95%CI 1.03-1, 95),

t(210)=6.46, p=0.001).

Table 2 presents the average CV% for all the mathematical models, with a variation ranging from 14%-30%. The mean CV% for the PaO2/FiO2 and PaO2/ PAO2 was 14%, which is considered a low variation compared to the RI with a mean CV% of 30%.

Table 2 Mean of CV% for the mathematical models

Mathematical Models	Min	Mean	SD	Max	CV%
PaO2/FIO2	46	256	36	714	14%
PaO2/PAO2	7%	43%	6%	125%	14%
OSI	2	7	1	30	19%
P(A-a)O2	12	209	44	600	21%
OI	1	7	2	44	23%
RI	0.13	2.30	0.68	13.48	30%

PaO2/FIO2 arterial oxygen tension to inspired oxygen fraction, PaO2/PAO2 arterial/alveolar oxygen tension ratio, OSI Oxygen saturation index, P(A-a)O2 alveolar-arterial oxygen tension difference, OI Oxygen index, RI respiratory index.

Discussion and conclusion

This study examined the variability of the currently used mathematical models for the pulmonary gas exchange during a short period, under the assumption of lung status stability. This finding indicated a variation ranging from 14%-30%, in which the RI exhibited the highest and the PaO2/FiO2 and PaO2/ PAO2 the lowest variation.

Over the past 60 years, many mathematical models proposed to measure the pulmonary oxygenation status accurately. However, models should be straightforward, accurate, informative, feasible, and cost-effective.[11,17] Gould highlighted the essential characteristics to develop a perfect oxygenation model; a) The mathematical model must be reliable under stable conditions, it should present the same value with repetition. b) The model must work for what it purports to measure. c) The model must respond to physiological changes with acceptable sensitivity. d) The model should present valuable clinical progress or diagnosis. Common models of oxygenation have historically consisted of content-based venous admixture (Qs/Qt) or tension-based models. This study demonstrated the need for a comprehensive index that can adequately take in consideration the effect that factors, independent of the pulmonary configuration, have on the PaO2 values to ensure that the condition of a patient's lung is more adequately represented and an accurate treatment plan is developed.

Literature demonstrated that the currently used oxygen mathematical modeling vary in reflecting the pulmonary status of the affected patient.[2,18,19] The mathematical

models implied a change in the patient's lung status as they fluctuate with external physiological factors. This can misrepresent the definition of the lung status.[2] The variation in the currently used mathematical models of oxygenation appears in the presence of true-shunt-poor defects.

Based on the findings of this study, the PaO2/FiO2 ratio variation was lower compared to other mathematical models.[1,2,20] This finding is consistent with the Gowda et al. study in which the authors examined the variation of FiO2 on the PaO2/FiO2 ratio, PaO2/PAO2, P (A-a) O2, RI, and content-based venous admixture Qs/Qt. They reported a variation in the models with changes in FiO2 between 21% to 100%, and the PaO2/FiO2 ratio was associated with a lower variation, compared to the other models.[21] This suggested using the PaO2/FiO2 ratio as an indicator to monitor patients who received FiO2 ≥ 50% in usual clinical conditions as this variation varied significantly for the patients with ventilation-perfusion abnormalities.[21]

However, many studies used simulated sophisticated computational models to investigate the mathematical modeling behavior in patients with lung damage. The studies indicated that a substantial variation occurred with the FiO2 and C(a–v̄) O2, except for Qs/Qt, where the change was <2%. A simulated study used a validated physiology simulator to examine the variation of the Qs/Qt, RI, PaO2/FiO2 ratio, and A-a gradient while changing the FiO2, PCO2, and Hb2,[14]. The author divided their simulated samples in two groups, a true-shunt-rich and true-shunt-poor lung configuration and reported that the Qs/Qt, RI, PaO2/FiO2 ratio, and A-a gradient models varied with changes in the external factors, except the Qs/Qt, which had a slight variation of 30% during the FiO2 changes. Another simulated study using a computational model reported that the Qs/Qt had the lowest model variation with 5.1% compared to Qs/Qt, RI, PaO2/FiO2 ratio, A-a gradient when examined with variations induced by four factors, Hb, FiO2, VO2, and PaCO2, without changing the lung configuration.[14] Even though studies showed that the Qs/Qt was the most reliable model to assess pulmonary oxygenation, the technical difficulty associated with the direct sampling of mixed venous blood limits its practicality. Nevertheless, there is a need for additional clinical trials to determine the robustness of these models with a varied population and different pulmonary diseases.

Strength and limitations

The findings of this study should be interpreted with caution. We hypothesized that the patient's lung characteris-

tics would have remained stable within the 120-minute window as reflected by the arterial blood sample, irrespective of varying FiO2 or other mechanical ventilator settings. This could be justified by the notion that dramatic changes in the lung condition are less likely to happen within such a short period of time (average of 34 minutes). However, a decisive comparison cannot be made due to the unavailability of continuous data on the hemodynamic status (other than the initial measurement) for the patients. Besides the insufficient data of the hemodynamic status, other possible factors, such as patient's positioning (e.g., turning and morning care), specific procedures (e.g., endotracheal suctioning), level of comfort (e.g., pain management) could have significantly attributed to the inconsistency of the mathematical model. In addition, the observational nature of this study would limit the validity of the results.

However, the data of this study were collected from different ICUs, including patients with a variety of pathologies. Although this variation in the baseline characteristics of the study sample would limit the interpretation of the findings, we aimed to describe the variation of the mathematical modeling of the oxygen status irrespective of the underlying conditions. Future studies should be specific for a subtype of pulmonary pathology. The model should consider the complexity of the lung physiology, measure the oxygenation independent of FiO2, assess whether the breathing process is dynamic, and determine the non-linear relationship between oxygen tension and content.11,17

In conclusion, even though oxygen models have potential benefits, our results indicated the need to adopt a new model that mathematically integrates pulmonary physiological factors to represent an actual lung condition. This will support other oxygen models to assess the severity of the respiratory illness.

Conflict of Interest

The authors declare that they have no conflict of interest.

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None.

Declarations

This manuscript is an original work and is not under consideration for publication by other journals. Some of this study's findings have been presented as abstract for American Association of Respiratory Care Congress in USA Nov 2021.

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