ORIGINAL ARTICLE

Estimating the best fraction of inspired oxygen for calculation of PaO2/FiO2 ratio in acute respiratory distress syndrome due to COVID-19 pneumonia

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Background: The ratio of partial pressure of oxygen in arterial blood (PaO2) to the fraction of inspiratory oxygen concentration (FiO2) is an indicator of pulmonary shunt fraction. PaO2/FiO2 (P/F) ratio is used to classify severity of acute respiratory distress syndrome (ARDS). With the same shunt fraction, P/F ratio decreases with increases in FiO2 which may lead to errors in classifying severity of ARDS. The effect of FiO2 on P/F ratio has not been investigated in COVID-19 pneumonia. In this study, we estimated the best FiO2 for the calculation of P/F ratio in a sample of patients with ARDS due to COVID-19 pneumonia. **Materials and Methods:** Blood gas and ventilatory data of 108 COVID-19 ARDS patients were analyzed in a cross-sectional observational study. Using Oxygen Status Algorithm the calculated shunt fraction served a basis for calculating P/F ratio for different FiO2. The severity of ARDS determined by P/F ratios at each FiO2s was compared with the shunt-based severity to find the optimum FiO2 for calculation of P/F ratio so the resulting classification has the best match with the reference classification. **Results:** A FiO2 of 1.0 for calculation of P/F ratio and ARDS classification showed the best match with shunt-based ARDS classification. A regression model was obtained with the PaO2, patient's original FiO2, Hemoglobin concentration, and SaO2 as the independent predictors of the P/F ratio for the FiO2 of 1.0. **Conclusion:** This study shows a FiO2 of 1.0 as the best value for correct calculation of P/F ratio and proper classification of ARDS.

Key words: Acute respiratory distress syndrome, COVID-19, mechanical ventilation, oxygenation indices, P/F ratio, pulmonary shunt

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INTRODUCTION

A fundamental step in the management of patients with arterial hypoxia is to assess the extent of damage to the gas exchange function of the lungs. The measurement of pulmonary shunt fraction which is defined as the fraction of mixed venous blood bypassing oxygenation in the lung capillaries is the most accurate method to quantify the extent of pulmonary damage.[1]

The reason why shunt fraction is the best indicator of lung involvement associated with oxygenation disturbances lays in its independence from inspired oxygen concentration and the type of oxygenation deficit.[2] Clinical measurement of shunt fraction requires insertion of pulmonary artery catheter to obtain mixed venous blood sample from pulmonary artery, which unfortunately is a risky procedure especially in critically ill patients and therefore is not feasible under most clinical conditions.[3] Therefore, clinicians use the ratio of oxygen partial pressure in arterial blood (PaO2) to inspiratory fraction of oxygen (FiO2) as a surrogate for pulmonary shunt fraction.[4] In healthy controls, PaO2/FiO2 (P/F) ratio varies from 400 to 500 at sea level and reduces with decreasing barometric pressure.[5,6] The

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Berlin definition uses P/F ratio for classification of acute respiratory distress syndrome (ARDS) into mild (200 < P/F ratio ≤300), moderate (100 < P/F ratio ≤200), and severe (P/F ratio ≤100) form of the syndrome.[7] Unfortunately with the same value of shunt fraction the P/F ratio varies with the value of FiO2 at which the PaO2 is measured.[8] Therefore its value as a surrogate for pulmonary shunt fraction and as a discriminating factor for ARDS classification significantly deteriorates with changes in the FiO2. For example, at a fixed pulmonary shunt of 40% the P/F ratio would be 220 (mild ARDS) and 64 (severe ARDS) at FiO2 of 0.21 and 1.0, respectively.[9]

A previous study on ARDS, showed considerable discrepancies in severity categorization using P/F ratios corrected for FiO2 compared to noncorrected values.[10] The effect of FiO2 on P/F ratio has not been investigated previously. Since FiO2– PaO2 relationship may be different in COVID-19 induced pneumonia it's necessary to investigate the effects of FiO2 on P/F ratio and the consequences on ARDS classification in ARDS cases due to COVID-19 pneumonia. COVID-19 induced pneumonia and ARDS has been a major challenge since the start of the pandemics and necessitates special attention.[11,12] In this study on a sample of adult patients with COVID-19-induced ARDS patients, we used blood gas and ventilatory data of patients together with Oxygen Status Algorithm (OSA) to calculate P/F ratios for a range of FiO2s and compared the resultant severity categorization with the severity classification defined by the estimated shunt fraction to obtain the optimum FiO2 for calculation of P/F ratio.

MATERIALS AND METHODS

Ethics committee of Research Department, Isfahan University of Medical Sciences approved the study (IR. MUI. MED. REC.1399.1010). In this cross-sectional observation study, blood gas and ventilatory data collected from mechanically ventilated patients with COVID-19-induced ARDS. Pregnant patients, patients with cardiovascular disorders, history of chronic respiratory disease, heavy smoking, history of mechanical ventilation in the last year, and those on drugs influencing pulmonary shunt (hydralazine, dopamine, dobutamine, and nitrate-containing substances) excluded from the study.

All patients were under mechanical ventilation using SIMV mode with lung protecting strategy. A tidal volume = 4–6 ml/kg, positive end-expiratory pressure = 5–10 cmH2O, and respiratory rate manipulated according to the level of arterial partial pressure of CO2.

Oxygen status algorithm

OSA version 3.0 is a Windows program developed by Siggaard-Andersen and coworkers.[13] OSA estimates the acid-base and oxygen status of the blood and displays the results in the form of charts, graph, blood gas map, and diagram. It also allows changing some respiratory parameters and studying the effects on others parameter while keeping some parameters constant. This application has been used extensively as a laboratory, research, and clinical tools for studying and managing acid-base and oxygen status of patients, especially in the intensive care unit. Blood gas and ventilatory data of the patient must be entered directly into the program using main program window or inputted as a data file. The barometric pressure of the area must be entered into the program and the program corrects all calculated values for the barometric pressure at the sea level (760 mmHg).[14] We entered patient blood gas and ventilatory data into the application, and then recorded the shunt fraction calculated by the program. In the next step, we kept shunt fraction constant in the program and changed FiO2 from 0.2 to 1.0 in increments of 0.1. After each change in FiO2, the calculated values for PaO2 and the resulting P/F ratio were recorded. Therefore for each patient, nine different values of P/F ratio for different values of FiO2 were simulated.

Severity categorization

For each estimated P/F ratio obtained from OSA the severity of ARDS was determined based on the threshold values recommended by Berlin definition task force[7] as shown in Table 1. As the reference classification, the severity of ARDS in each patient was determined by using the threshold values for shunt fraction defined in the Berlin definition specifications [Table 1].[7]

Statistical analysis

A sample size of 84 was calculated using the following formula for a confidence level of 80%, a margin of error equal to 5% using previously reported value of 70 as the P/F ratio standard deviation (s) (SD)[2,15] to estimate the mean P/F ratio with an error of 15.

$$N = \frac{\left(Z_{1-\frac{a}{2}}\right)^2 \times S^2}{d^2} = \frac{(1.96)^2 \times 70^2}{15^2} = 83.66 \approx 84$$

Table 1: Thresholds of PaO2/FiO2 ratio and shunt fractions for classification of acute respiratory distress syndrome

ARDS category	Definition
No ARDS	P/F ratio>300 Shunt<16%
Mild	200<P/F ratio≤300 16%≤ shunt<26
Moderate	100<P/F ratio≤200 26%≤ shunt<32
Severe	P/F ratio≤100 Shunt≥32%

P/F ratio=PaO2/FiO2 ratio; ARDS=Acute respiratory distress syndrome

Resulting classifications for each value of P/F ratio associated with each hypothetical FiO2 were compared with reference classification based on shunt fraction to calculate the proportions of correct and wrong classifications. The proportions of correct and wrong classifications for each FiO2 were compared with each other using Chi-square statistics together with Spearman correlations to measure the association between P/F ratio-based classifications and reference classification. Multiple linear regression analysis used to build a model for predicting simulated P/F ratio based on blood gas data. We used SPSS version 26 for statistical analysis. A $P < 0.05$ was considered statistically significant. Data were presented as mean ± SD or *n* (%) where applicable. The SPSS data were exported as comma-delimited file which used by a python script to produce appropriate data files for input into OSA application.

RESULTS

A total of 108 (51 male and 48 female) 20–90 years' old (61.8 ± 13.7) cases were studied. Data from nine cases had missing values and therefore excluded from the analysis. PaO2 ranged from 30 to 90 mmHg (66 ± 24), FiO2 from 0.30 to 1.0 (0.76 ± 0.24), P/F ratio from 30 to 428 (109 ± 86). Demographic data and clinically measured ventilatory parameters are summarized in Tables 2 and 3 which shows a wide range of shunt fractions and P/F ratios.

Calculated pulmonary shunt for each patient ranged from 1.35% to 69.5% (34 ± 15.6).

Using shunt-based severity as the reference for severity classification showed that the best match belonged to P/F ratio for an FiO2 of 1.0 ($P/F_{1.0}$) [Figure 1, and Table 4]. Using an FiO2 of 1.0, severity of the ARDS classified correctly for 84 patients (84.8%, 95% confidence interval 76–91, Spearman correlation® of 0.944, $P < 0.001$). The worst classification was with FiO2 of 0.20 with only 26 patients classified correctly (26.3, 95% confidence interval [CI], 18–36, $r = 0.722$, $P < 0.001$).

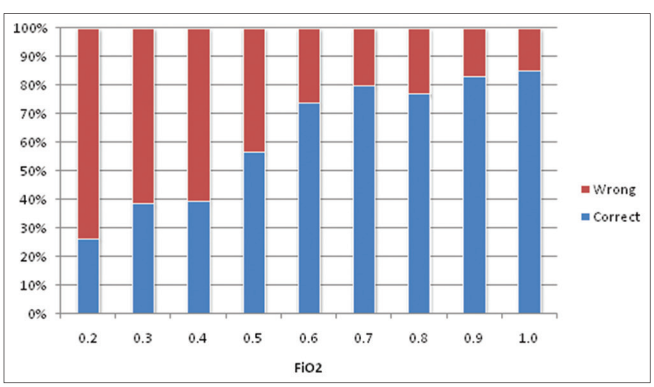

Figure 1: Proportions of correct and wrong ARDS classifications among different types of P/F ratios. ARDS = Acute Respiratory Distress Syndrome; FiO2 = Fraction of Inspiratory Oxygen

Multiple regression analysis with $P/F_{1.0}$ as dependent variable showed PaO2, patient's original FiO2, hemoglobin concentration (Hb), and oxygen saturation of hemoglobin (SaO2) as the independent predictors ($R^2 = 0.882$, $P = 0.000$). Regression coefficients for these predictor variables yielded the following model:

$$P/F_{1.0} = 393 + 5.426 \times PaO2 - 237.2 \times FiO2 - 8.134 \times Hb - 3.769 \times SaO2$$

Table 2: Different demographic, blood gas, and ventilatory data of the patients (*n*=99)

Variable	Value
Male	51 (51.5)
Female	48 (48.5)
Age (years)	61.8±13.7 (20-90)
PaO2 (mmHg)	66±24 (30-90)
SaO2 (%)	87±9.6 (51-97)
FiO2	0.76±0.24 (0.30-1.0)
PaO2/FiO2	109±86 (30-428)
PaCO2 (mmHg)	53±18.5 (19-135)
pH	7.30±0.08 (7.06-7.59)
Hemoglobin (g/dL)	11±2.3 (5.1-18.2)
Pulmonary shunt (%)	34±15.6 (1.35-69.5)
Static compliance (ml/cmH2O)	41±29 (5-150)
Airway resistance (cmH2O/L/s)	10.4±6 (1-34)
Peak inspiratory pressure (cmH2O)	28±8.4 (11-50)
Positive end-expiratory pressure (cmH2)	8.8±3.4 (5-25)
Mean airway pressure (cmH2O)	15.7±4.7 (6-27)
Minute ventilation (L/min)	11±2.9 (4.4-17.5)
Total respiratory rate (breath/min)	25±7.7 (10-54)
Mechanical ventilation mode	
SIMV	81 (81.8)
A/C	10 (10.1)
SPV	8 (8.1)

Data are mean±SD (minimum-maximum) or *n* (%) where applicable. SD=Standard deviation; SIMV=Synchronized Intermittent Mandatory Ventilation; A/C=Assist/Control; PSV=Pressure Support Ventilation

Table 3: Estimated PaO2/FiO2 ratio and proportions of correct classifications associated with each value of PaO2/FiO2 ratio

FiO2	Mean±SD (range) [a]	Correct classifications (%)	Spearman correlation[b]
0.2	235±74 (50-480)	26 (26.3, 18-36)	0.722
0.3	193±83 (88-528)	38 (38.4, 29-49)	0.823
0.4	165±97 (69-564)	39 (39.4, 30-50)	0.677
0.5	150±112 (56-591)	56 (56.6, 46-67)	0.732
0.6	144±126 (47-611)	73 (73.7, 64-82)	0.862
0.7	141±138 (41-626)	79 (79.8, 71-87)	0.934
0.8	142±148 (37-638)	76 (76.8, 67-85)	0.903
0.9	146±157 (34-656)	82 (82.8, 74-90)	0.912
1.0	152±165 (31-653)	84 (84.8, 76-91)	0.944

Data are mean±SD or *n* (%) 95% CI. [a]All P/F ratios calculated using oxygen status algorithm corrected to a barometric pressure of 760 mmHg (11), [b]All correlations were significant at $P<0.001$ value. P/F ratio: PaO2/FiO2 ratio. SD=Standard deviation; CI=Confidence interval

Table 4: Proportions of acute respiratory distress syndrome severity based on shunt fraction and PaO2/FiO2 ratio with FiO2 of 1.0

Shunt fraction	$P/F_{1.0}$				
	Severe	Moderate	Mild	No ARDS	Total
Severe	56 (56.6)	0	0	0	56 (56.6)
Moderate	8 (8.1)	8 (8.1)	0	0	16 (16.2)
Mild	0	6 (6.1)	7 (7.1)	1 (1)	14 (14.1)
No ARDS	0	0	0	13 (13.1)	13 (13.1)
Total	64 (64.7)	14 (14.1)	7 (7.1)	14 (14.1)	99 (100)

Data are *n* (%). $P/F_{1.0}$=PaO2/FiO2 ratio with FiO2 of 1.0; ARDS=Acute respiratory distress syndrome

DISCUSSION

The result of this study shows the $P/F_{1.0}$ as an accurate measure for ARDS classification. Using $P/F_{1.0}$ for ARDS classification yields an accuracy of about 85% compared to reference classification using pulmonary shunt fraction, while P/F ratios associated with FiO2 ≤ 0.4 lead to accuracies lower than 40%. Indeed with increasing FiO2 the rate of correct classification increases from <30% to about 85% which means that with increasing FiO2 the calculated P/F ratio tends to be more correlated with the shunt fraction. Further experiments are required to study the effect of increasing inspiratory oxygen concentration on the accuracy of P/F ratio for classification of ARDS severity using experimental measurement of pulmonary shunt fraction.

The range of FiO2 used in this study was wide enough to make obtaining a correlation with shunt level possible. Shunt fractions also showed a wide range suitable for the purpose of this study.

Shunt fraction estimated by OSA used in this study as the reference for ARDS severity classification. OSA has been used and validated extensively as a reliable tool for the estimation of gas exchange and acid-base parameters.[15-25]

This study involved ARDS cases resulted from COVID-19. Previous studies had shown the effects of varying FiO2 on the P/F ratios and on the resultant ARDS classifications in classic form of ARDS.[8,10] The result of the present study shows the same effect for FiO2 on P/F ratio and ARDS classification in COVID-19 pneumonia.

COVID-19 may involve the lungs and produces a wide spectrum of respiratory failure with limited therapeutic options at hand. Correct classification of COVID-19 induced ARDS severity based on P/F ratio may be important with respect to the provision of early invasive treatment options such as intubation, mechanical ventilation, prone position, and extracorporeal membrane oxygenation.[26] We recommend using measured $P/F_{1.0}$ for the classification of ARDS severity. If the clinical measurement of $P/F_{1.0}$ is not feasible, one may use the regression model presented in this study to estimate $P/F_{1.0}$. To determine the usefulness and the accuracy of the predictive model developed in this study for estimation of $P/F_{1.0}$, further clinical experiments on ARDS patients are necessary.

A possible limitation in the generalization of the result of this study is the fact that all enrolled cases were COVID-19 induced ARDS, while this may not significantly invalidate the study results, further study on non-COVID-19 cases and comparison with COVID-19 patients helps to shed more lights on the ARDS classification. Another concern is the fact that in addition many patients in this study were older than 60 years. Since the value of PaO2 normally decreases with increasing age. Although the magnitude of this error is not large in patients under mechanical ventilation, anyhow this may lead to small errors when calculating P/F ratio.

CONCLUSION

ARDS severity classification using $P/F_{1.0}$ shows the best match with the shunt-based classification. In addition, it is possible to use the regression model equation from this study to estimate the value of $P/F_{1.0}$ when its clinical measurement is not practical.

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Conflicts of interest

There are no conflicts of interest.

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