Comparison of the Oxygenation Factor and the Oxygenation Ratio in Subjects With ARDS

Mohamad F El-Khatib, Imad J Bouakl, Chakib M Ayoub, Robert L Chatburn, Hatem Farhat, Mayyas Msheik, Mohamad H Fakih, and Ali H Hallal

BACKGROUND: The oxygenation ratio (ie, P_{aO_2}/F_{IO_2}) remains the most commonly used index for assessing oxygenation and disease severity in patients with acute ARDS. However, the oxygenation ratio does not account for mechanical ventilation settings. We hypothesized that the oxygenation factor (ie, oxygenation ratio/mean airway pressure) is superior to the oxygenation ratio in reflecting oxygenation in patients with ARDS and results in a different classification of ARDS severity. METHODS: In 150 subjects with ARDS (50 severe, 50 moderate, and 50 mild), arterial blood gas, mean airway pressure, static lung compliance, driving pressure, and mechanical power were obtained. The oxygenation ratio and the oxygenation factor were then calculated. Receiver operating characteristic curves were constructed for oxygenation ratio and oxygenation factor at lung compliance > 40 mL/cm H_2O, driving pressure < 15 cm H_2O, and mechanical power < 17 J/min, thresholds that are known to predict survival in patients with ARDS. Subjects were reclassified for ARDS severity on the basis of the oxygenation factor and compared to classification on the basis of the oxygenation ratio. RESULTS: Areas under the receiver operating characteristic curves for the oxygenation factor were significantly higher than for the oxygenation ratio. Reclassification of ARDS severity using the oxygenation factor did not affect subjects classified as having severe ARDS per the oxygenation ratio. However, 52% of subjects with moderate ARDS per the oxygenation ratio criteria were reclassified as either severe (25 subjects) or mild ARDS (1 subject) on the basis of oxygenation factor criteria. Also, 54% of subjects with mild ARDS per the oxygenation ratio criteria were reclassified as severe (4 subjects), moderate (21 subjects), or non-ARDS (2 subjects) on the basis of oxygenation factor criteria. CONCLUSIONS: The oxygenation factor was a superior ARDS oxygenation index compared to the oxygenation ratio and should be considered as a substitute criteria for classification of the severity of ARDS. (ClinicalTrials.gov registration NCT03946189.) *Key words: acute respiratory distress syndrome; oxygenation ratio; oxygenation index; mechanical ventilation; mean airway pressure; driving pressure; mechanical power.* [Respir Care 2020;65(12):1874–1882. © 2020 Daedalus Enterprises]

Introduction

The oxygenation ratio, defined as P_{aO_2}/F_{IO_2}, was first described by Horovitz et al[1] in 1974, and since then it has remained the most commonly used index for the assessment of oxygenation status in patients with respiratory distress/failure.[2,3] The oxygenation ratio has also been used consistently to assess the effectiveness of different ventilatory support

Dr El-Khatib, Dr Ayoub, and Mr Fakih are affiliated with the Department of Anesthesiology, American University of Beirut, Beirut, Lebanon. Dr Bouakl is affiliated with the Department of Internal Medicine, American University of Beirut, Beirut, Lebanon. Mr Chatburn is affiliated with the Respiratory Institute, Cleveland Clinic, Cleveland, Ohio. Drs Farhat, Msheik, and Hallal are affiliated with the Department of Surgery, American University of Beirut, Beirut, Lebanon.

Drs El-Khatib and Bouakl are co-first authors.

Mr Chatburn discloses relationships with IngMar Medical and Vyaire Medical. The remaining authors have no conflicts to disclose.

Correspondence: Ali H Hallal MD FRCS FACS, Department of Surgery, American University of Beirut, Beirut, PO Box 11-0236, 1107 2020, Lebanon. E-mail: ah05@aub.edu.lb.

DOI: 10.4187/respcare.07669

interventions (eg, use of PEEP, prone positioning, recruitment maneuvers) in patients with ARDS.[4-6]

In 2011, the Berlin definition for ARDS was developed and recommended the use of oxygenation ratio as the sole variable for differentiation of mild (oxygenation ratio 200–300 mm Hg), moderate (oxygenation ratio 100–200 mm Hg), or severe ARDS (oxygenation ratio $\leq$ 100 mm Hg).[7] However, the Berlin definition of ARDS did not elaborate on several important mechanical ventilation settings and only indicated that the PEEP had to be $\geq$ 5 cm H_2O for all 3 severity categories of ARDS.[7]

Villar et al[8] stated that the stratification of severity of ARDS subjects as proposed by the Berlin criteria is useless for assessing severity of lung injury and could be harmful for enrolling subjects into clinical trials. Furthermore, Villar et al[9,10] reported in 2 separate studies that the same subjects in a certain ARDS severity category can be reclassified to another ARDS severity category by adequate consideration of the mechanical ventilation settings. Hernu et al[11] could not validate the Berlin definition of ARDS, stating that neither stratification by severity nor by oxygenation ratio at study entry was independently associated with mortality. Thille et al[12] reported that the Berlin definition did not correlate with the presence of diffuse alveolar damage in > 50% of subjects categorized as having moderate or severe ARDS.

In light of the above findings, the oxygenation ratio index might not be a sensitive and accurate indicator of the severity of the lung disease or the oxygenation status, and it could be reasonably argued that 2 patients with exactly the same oxygenation ratios but different levels of mechanical support (ie, one patient with a mean airway pressure ($\overline{P}_{aw}$) of 10 cm H_2O vs another patient with a $\overline{P}_{aw}$ of 20 cm H_2O) should not be classified as having the same severity of oxygenation and ARDS. A recent national survey of > 400 multidisciplinary critical care providers proposed a consensus for defining severe and refractory hypoxemia as either an oxygenation ratio < 100 cm H_2O or P_{aO_2} < 60 mm Hg and F_{IO_2} > 0.7 for 1 h with PEEP $\geq$ 15 cm H_2O rather than any PEEP $\geq$ 5 cm H_2O.[13] As such, current data available from several studies support the need for a superior and standardized method or index for the evaluation of oxygenation status and severity of the disease in patients with ARDS rather than providing only 3 ranges for oxygenation ratio and stating that PEEP should be $\geq$ 5 cm H_2O for all 3 of these ranges.[8-13]

We previously described an oxygenation index as

$$OF = \frac{OR}{\overline{P}_{aw}} = \frac{P_{aO_2}}{F_{IO_2} \times \overline{P}_{aw}}$$

where OF is the oxygenation factor and OR is the oxygenation ratio.[14] The oxygenation factor, which normalizes the oxygenation ratio to $\overline{P}_{aw}$, takes into consideration important mechanical ventilatory support variables such as PEEP, inspiratory:expiratory ratio, and tidal volume (V_T) or inspiratory pressure.[15] Our study showed that the oxygenation factor was more reliable than oxygenation ratio in reflecting intrapulmonary shunt in subjects undergoing coronary artery bypass grafting and with no underlying lung disease.[14] In patients with ARDS, the oxygenation factor could be a better discriminator than oxygenation ratio for reflecting oxygenation status and severity of ARDS simply because the oxygenation factor incorporates an index of the level of ventilatory support (ie, $\overline{P}_{aw}$), whereas the oxygenation ratio does not.

The aim of this study was to compare the diagnostic decision-making quality of the oxygenation factor to that of the oxygenation ratio when used with 3 important predictors of mortality in patients with ARDS: static compliance,[16] driving pressure,[17] and mechanical power.[18] We hypothesized that the oxygenation factor is superior to the oxygenation ratio in differentiating patients with ARDS around critical thresholds of lung compliance, driving pressure, and mechanical power. A secondary hypothesis was that the distribution of patients classified as having mild, moderate, or severe ARDS on the basis of the oxygenation ratio would differ from the classification made on the basis of the oxygenation factor.

QUICK LOOK

Current knowledge

The oxygenation ratio, which is the ratio of P_{aO_2} to F_{IO_2}, is the most commonly used indicator for oxygenation in patients with ARDS. It is also an important component of the Berlin definition for ARDS, and its value is the main differentiator between mild, moderate, or severe ARDS. However, the oxygenation ratio does not account for mechanical ventilation settings. We hypothesized that the oxygenation factor (ie, oxygenation ratio/mean airway pressure) is superior to the oxygenation ratio in reflecting oxygenation in patients with ARDS.

What this paper contributes to our knowledge

When the oxygenation ratio was normalized to the mean airway pressure, which is a major indicator of severity of mechanical ventilation settings, the resulting oxygenation factor provided a stronger reflection of major ARDS mortality indicators such as mechanical power, driving pressure, and static lung compliance than the oxygenation ratio.

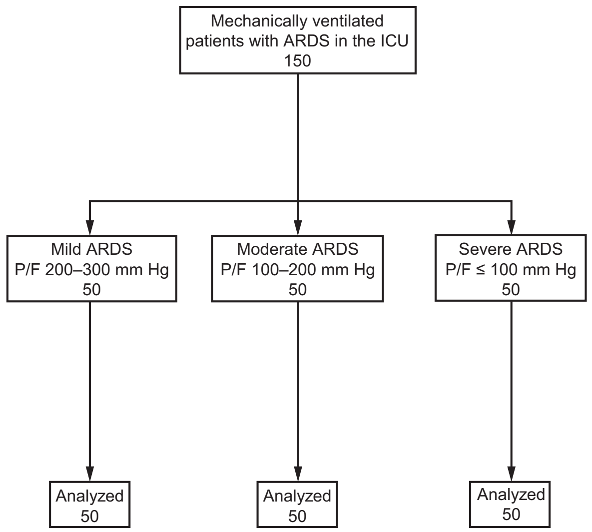

Fig. 1. Flow chart. P/F = P_{aO_2}/F_{IO_2}

Methods

Study Design and Population

We included 150 hemodynamically stable subjects of both genders, > 18 y old and receiving invasive mechanical ventilation in the ICU for respiratory distress/failure (ie, 50 subjects with oxygenation ratio ≤ 100 mm Hg, 50 subjects with oxygenation ratio 100–200 mm Hg, and 50 subjects with oxygenation ratio 200–300 mm Hg) in this study (Fig. 1). Enrollment was not consecutive, and subjects were included based on their P_{aO_2}/F_{IO_2} values. Once 50 subjects of a certain category of ARDS severity were obtained, enrollment stopped for that category. Patients from whom arterial blood samples could not be obtained for arterial blood gas analysis and patients with no adequate and reliable pulse oximetry measurements were excluded from the study. We also excluded patients receiving extracorporeal membrane oxygenation or patients who were placed in the prone position. All subjects were monitored with continuous electrocardiography, blood pressure, and pulse oximetry. All subjects were ventilated with a lung-protective strategy with mechanical ventilation settings selected and applied by the medical team in charge of the medical care of the subjects, with no interference from the research team.

After intubation and initiation of invasive mechanical ventilation, a period of 2–6 h was allowed for the subject to achieve steady state on the mechanical ventilator before any data collection. During this time, the subjects were not disturbed by nursing procedures and were not disconnected from the ventilator for any reason. After the stabilization period, arterial blood samples were collected on all subjects using the same model of syringe (Pre-set Vacutainer System, Beckton-Dickinson, Plymouth, United Kingdom). Arterial blood samples were immediately subjected to duplicate blood gas analysis in 2 separate blood gas machines (RAPIDPoint 500, Siemens Healthcare Diagnostics, Newark, Delaware) and the average P_{aO_2} value from the duplicate measurements was used for further calculations.

Basic demographic variables including age, height, weight, gender, and primary disease were collected. The ventilatory support parameters, namely mode of ventilation, breathing frequency, V_T, plateau pressure (P_{plat}), inspiratory time, expiratory time, PEEP, and $\overline{P}_{aw}$, which are readily available from the mechanical ventilator, were collected when the arterial blood samples were obtained. Additionally, the driving pressure (ΔP; measured as P_{plat} minus total PEEP, where total PEEP = set PEEP + auto-PEEP), the static lung compliance (measured as $V_T/\Delta P$), and the mechanical power (determined as described previously[19,20]) were also collected for all subjects. This study was approved by the Institutional Review Board at the American University of Beirut, and informed written consent was obtained from the subjects' legal guardians.

Study Measurements

For each subject the oxygenation ratio was calculated as P_{aO_2}/F_{IO_2}, and the oxygenation factor was calculated as $P_{aO_2}/(F_{IO_2} \times \overline{P}_{aw})$. The receiver operating characteristic curves were created to describe the predictive performances of the oxygenation ratio and the oxygenation factor when using a threshold of 15 cm H_2O for the driving pressure,[17] a threshold of 17 J/min for the mechanical power,[18] and a threshold of 40 mL/cm H_2O for the static respiratory system compliance.[16] These thresholds have been shown to best differentiate between survival and death of patients with ARDS receiving mechanical ventilation.[16-18]

Furthermore, new criteria based on the oxygenation factor were created by (1) identifying the mean values for oxygenation factor that corresponded to the classification ranges based on the oxygenation ratio, then (2) creating range cutoff values by adding 2 standard deviations to the mean oxygenation factor values. Subsequently, all subjects originally stratified for ARDS severity based on the oxygenation ratio criteria were reclassified for ARDS severity based on the oxygenation factor criteria. Then the percentages of subjects who were reclassified from one ARDS category to another using the new oxygenation factor criteria were calculated.

Statistical Analysis

Normally distributed continuous variables were summarized as means ± SD, and non-normally distributed variables were summarized with medians and 25–75% interquartile range (IQR). Analysis of variance was used for the

Table 1. Subject Demographics and Ventilatory Support Parameters

	Oxygenation Ratio			P
	≤ 100 mm Hg	100–200 mm Hg	200–300 mm Hg	
Age, y	60 ± 20	63 ± 22	64 ± 21	.18
Gender (male/female)	21/29	32/18*	28/22	.09
Body mass index, kg/m^2	28 ± 5	28 ± 4	27 ± 4	.71
V_T, mL	432 ± 72	457 ± 81	465 ± 56	.06
V_T/ideal body weight, mL/kg	7.3 ± 1.1	7.1 ± .9	7.7 ± .9†	.008
Oxygenation ratio, mm Hg	78 ± 15	150 ± 27*	251 ± 31*†	< .001
Oxygenation factor, mm Hg/cm H_2O	4.3 ± 2.5	10.6 ± 4.8	20.3 ± 6.4*†	< .001
Breathing frequency, breaths/min	24 ± 2	19 ± 3*	17 ± 4*†	< .001
F_{IO_2}, %	89 ± 14	66 ± 21*	47 ± 14*†	< .001
PEEP, cm H_2O	9 ± 3	8 ± 3	6 ± 2*†	< .001
$\overline{P}_{aw}$, cm H_2O	22 ± 9	17 ± 8*	14 ± 6*	< .001
P_{plat}, cm H_2O	29 ± 7	25 ± 8*	21 ± 6*†	< .001
ΔP, cm H_2O	20 ± 7	17 ± 7*	15 ± 5*	.001
Mechanical power, J/min	33 ± 10	24 ± 9*	18 ± 8*†	< .001
Compliance, mL/cm H_2O	25 ± 10	32 ± 15*	34 ± 15*	.001

Data are presented as mean ± SD. Oxygenation Ratio ≤ 100 mm Hg: $n = 50$; 100–200 mm Hg: $n = 50$; 200–300 mm Hg: $n = 50$; * $P < .05$ versus oxygenation ratio ≤ 100 mm Hg; †$P < .05$ versus oxygenation factor 100–200 mm Hg; V_T = tidal volume; $\overline{P}_{aw}$ = mean airway pressure; P_{plat} = plateau pressure; ΔP = driving pressure

comparison of continuous data. Areas under the curves were determined for all receiver operating characteristic curves. Sample size determination was based on a power analysis considering a type-1 error of 5%, a type-2 error of 20% (ie, power of 80%), a historical area under the curve of 0.62 for the oxygenation ratio, and an expected area under the curve of 0.8 for the oxygenation factor and indicated that ≥ 148 subjects were needed. We elected to include 150 subjects. SPSS software (IBM, Armonk, New York) was used for data analysis. STATA 14 software (StataCorp, College Station, Texas) was used to compare the areas under the receiver operating characteristic curves for a statistical comparison between any 2 receiver operating characteristic curves. Statistical significance was considered at $P < .05$.

Results

Subject demographics and ventilator support parameters are presented in Table 1. All subjects were ventilated with adaptive pressure ventilation continuous mandatory ventilation (G5 Ventilator, Hamilton Medical AG, Switzerland). This ventilation mode is classified as pressure control continuous mandatory ventilation, which is the same classification as pressure-regulated volume control on other ventilators.[21] None of the subjects had auto-PEEP. Subjects with an oxygenation ratio < 100 mm Hg had the lowest respiratory system compliance, the highest breathing frequency, the highest F_{IO_2} requirements, the highest PEEP, the highest $\overline{P}_{aw}$, and subsequently the lowest oxygenation factor and the highest P_{plat}, ΔP, and mechanical power ($P < .05$) (Table 1).

As shown in Table 2 and Figure 2, the areas under the curve for the oxygenation factor using respiratory system compliance, driving pressure, and the mechanical power cutoff thresholds of 40 mL/cm H_2O, 15 cm H_2O, and 17 J/min, respectively, were significantly higher than the corresponding areas under the curve for the oxygenation ratio compliance (Fig. 2A vs Fig. 2D), driving pressure (Fig. 2B vs Fig. 2E), and mechanical power thresholds (Fig. 2C vs Fig. 2F) (Table 2).

The areas under the curve of the receiver operating characteristic curves for the oxygenation ratio and both the respiratory system compliance (0.601, 95% CI 0.504–0.698) and the driving pressure (0.616, 95% CI 0.526–0.706) were of similar predictive values. However, the area under the receiver operating characteristic curve of the oxygenation ratio and the mechanical power (0.877, 95% CI 0.821–0.933) was higher than the areas under the curve for oxygenation ratio and respiratory system compliance as well as for oxygenation ratio and driving pressure (Table 2).

Also, the area under the receiver operating characteristic curves for the oxygenation factor and both the respiratory system compliance (0.688, 95% CI 0.592–0.784) and driving pressure (0.698, 95% CI 0.614–0.781) were of similar predictive values. However, the area under the receiver operating characteristic curve of the oxygenation factor and the mechanical power (0.970, 95% CI 0.947–0.993) was higher than the areas under the curve for the oxygenation factor and respiratory system compliance as well as for oxygenation factor and driving pressure (Table 2).

The range of values for the oxygenation factor was 33 mm Hg/cm H_2O (minimum of 1 mm Hg/cm H_2O and a

Table 2. Area Under the Receiver Operating Characteristic Curves

	Oxygenation Ratio	Oxygenation Factor	*P*
Lung compliance at cutoff threshold of 40 mL/cm H_2O	0.601 (0.504–0.698)	0.688 (0.592–0.784)	< .001
Driving pressure at a cutoff threshold of 15 cm H_2O	0.616 (0.526–0.706)	0.698 (0.614–0.781)	< .001
Mechanical power at a cutoff threshold of 17 J/min	0.877 (0.821–0.933)	0.970 (0.947–0.993)	< .001

Data are presented as area under the receiver operating characteristic curve (95% CI). Oxygenation Ratio: $n = 150$; Oxygenation Factor: $n = 150$.

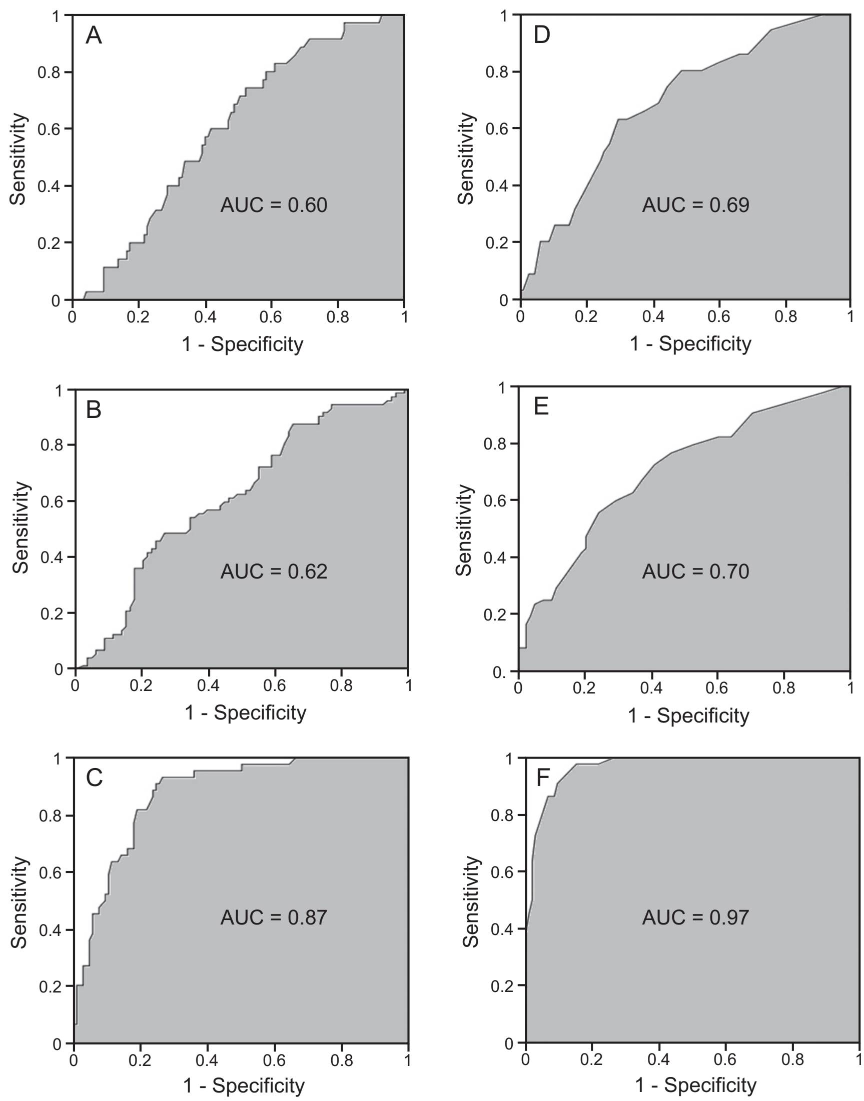

Fig. 2. Receiver operating characteristic curves for the oxygenation ratio (P_{aO_2}/F_{IO_2}) and (A) compliance, (B) driving pressure, and (C) mechanical power; and for the oxygenation factor ($P_{aO_2}/(F_{IO_2} \times \overline{P}_{aw})$) and (D) compliance, (E) driving pressure, and (F) mechanical power. $\overline{P}_{aw}$ = mean airway pressure; AUC = area under the curve.

maximum of 34 mm Hg/cm H_2O). An oxygenation factor based criteria for ARDS with 3 categories (ie, severe, moderate, and mild) and equal ranges for the oxygenation factor suggests that an oxygenation factor ≤ 10 mm Hg/cm H_2O indicates severe ARDS, an oxygenation factor 10–20 mm Hg/cm H_2O indicates moderate ARDS, and an oxygenation factor 20–30 mm Hg/cm H_2O indicates mild ARDS (Table 3).

Figure 3 shows the reclassification of ARDS severity in subjects based on the oxygenation factor criteria. Forty-nine subjects (98%) who were classified as severe ARDS based on the oxygenation ratio criteria remained as severe

Table 3. Classifications of ARDS Severity Based on Oxygenation Ratio and Oxygenation Factor

		Severe ARDS	Moderate ARDS	Mild ARDS	No ARDS
Oxygenation ratio, mm Hg	Classification ranges	≤ 100	100–200	200–300	> 300
Oxygenation factor, mm Hg/cm H_2O	Mean	4.3	10.6	20.3	NA
	SD	2.5	4.8	6.4	NA
	Mean + 2SD	9.3	20.2	33.1	NA
	Classification ranges	≤ 10	10–20	20–30	> 30

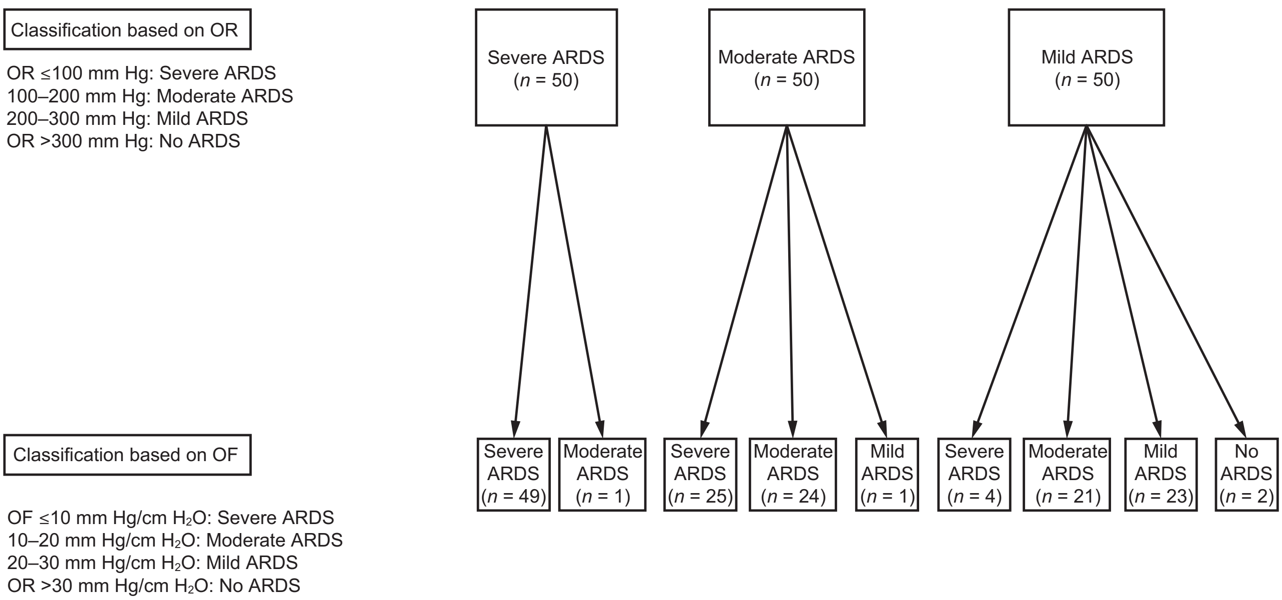

Fig. 3. Reclassification of subjects on the basis of the oxygenation factor. OR = oxygenation ratio; OF = oxygenation factor.

ARDS, whereas 1 subject (2%) was reclassified as moderate ARDS on the basis of the oxygenation factor criteria. Twenty-five subjects (50%) and 1 subject (2%) who were classified as moderate ARDS as per the oxygenation ratio criteria were reclassified as severe and mild ARDS, respectively, on the basis of the oxygenation factor criteria. Also, 4 subjects (8%), 21 subjects (42%), and 2 subjects (4%), who were classified as mild ARDS based on the oxygenation ratio criteria were reclassified as severe, moderate, and non-ARDS, respectively, as per the oxygenation factor criteria (Fig. 3).

Discussion

Our results indicate that the oxygenation factor, calculated as $P_{aO_2}/(F_{IO_2} \times \overline{P}_{aw})$, is superior to the oxygenation ratio (ie, P_{aO_2}/F_{IO_2}) in reflecting a mechanical power threshold of 17 J/min, but not for respiratory system compliance and driving pressure in subjects with ARDS. These results also indicate that the classification of ARDS severity might differ substantially with a classification criterion based on the oxygenation factor rather than the oxygenation ratio.

A major implication of this study is that perhaps the Berlin definition for ARDS should be revisited with the use of the oxygenation factor rather than the oxygenation ratio, both for determining oxygenation status and as the basis for stratifying the severity of patients with ARDS (ie, mild, moderate, severe). Previous studies have indicated that, in subjects with ARDS under specific ventilator settings, using the oxygenation ratio resulted in unreliable classification of lung injury and outcome.[22,23] Therefore, the oxygenation factor, by incorporating the ventilator settings into the oxygenation ratio, may be a more precise metric for classifying the oxygenation status and possibly the levels of lung injury in patients with ARDS. $\overline{P}_{aw}$ is an appropriate modifier for the oxygenation ratio because it reflects most of the mechanical ventilation parameters and settings (ie, PEEP, inspiratory time, expiratory time, V_T, or peak alveolar pressure).[15,24]

It is conceivable that appreciable changes in the oxygenation ratio will occur typically as a direct result of certain manipulations in the mechanical ventilation settings (eg, changes in PEEP, inspiratory:expiratory ratio, driving pressure, mechanical power), even when the patient's underlying condition has not changed.[25-27] This leads to imprecision in classifying the severity of ARDS for any particular patient, and thus makes comparison of patient groups more uncertain. Therefore, the PEEP level at which the oxygenation ratio is measured should be carefully specified when determining oxygenation status and diagnostic criteria for ARDS, and not just kept vague as indicated in the Berlin definition of ARDS (ie, any PEEP level ≥ 5 cm H_2O).[7]

When comparing the oxygenation factor and oxygenation ratio indices, we used important physiological and mechanical ventilation metrics such as static lung compliance, driving pressure, and mechanical power. Recent studies have shown the utility of such metrics in predicting mortality in patients with ARDS. Bellani et al[16] reported that higher driving pressure and lower respiratory system compliance were associated with increased mortality in 154 subjects with ARDS. Toufen Junior et al[28] reported that higher driving pressure was associated with worse long-term pulmonary function and structure in subjects with ARDS, even when the subjects were ventilated with a protective lung-ventilation strategy (ie, V_T of 4–8 mL/kg of ideal body weight and $P_{plat} \leq 30$ cm H_2O). In critically ill subjects receiving invasive ventilation for ≥ 48 h, Serpa Neto et al[18] noted that, even at low V_T, high mechanical power was independently associated with higher ICU mortality, 30-d mortality, ventilator-free days, and length of ICU and hospital stay. There was also a consistent increase in the risk of death with mechanical power > 17 J/min.[18] Parhar et al[29] and Gattinoni et al[30] suggested that mechanical power should guide our approach to mechanical ventilation, and it is only when a safe mechanical power cannot be achieved that other unconventional means of support, such as extracorporeal membrane oxygenation, should be pursued.

In this study, the predictive performances of both the oxygenation ratio and the oxygenation factor were higher and enhanced with the mechanical power at a threshold of 17 J/min compared to the driving pressure at a threshold of 15 cm H_2O and compared to the static compliance at 40 mL/cm H_2O, as reflected by the greater area under the receiver operating characteristic curve. This supports the hypothesis that mechanical power is a superior metric of the lung's oxygenation status and possibly of the severity of lung diseases compared to driving pressure or static lung compliance, as well as a better indicator of outcomes from mechanical ventilation, and that mechanical power should be considered as the most significant guiding factor for safe and efficient mechanical ventilation, with appropriate caveats.[29-31] On the other hand, we found no differences in the predictive performance of the oxygenation ratio or the oxygenation factor indices with the driving pressure at a threshold of 15 cm H_2O compared to static compliance at 40 mL/cm H_2O. This is not surprising because, from a mathematical point of view, the static compliance is nothing but the ratio of V_T (usually normalized to ideal body weight) to the driving pressure (assuming no auto-PEEP), whereas mechanical power incorporates not only the driving pressure but also other important ventilatory support parameters such as the breathing frequency, the inspiratory: expiratory ratio, and the airway resistance.[20]

Our results suggest that patients with ARDS and severe hypoxemia (ie, oxygenation ratio ≤ 100 mm Hg) should be considered to have severe ARDS regardless of the mechanical ventilation settings, given that using the oxygenation factor instead of the oxygenation ratio did not have any impact on the reclassification of these patients. However, patients with moderate ARDS (ie, oxygenation ratio 100–200 mm Hg) or mild ARDS (oxygenation ratio 200–300 mm Hg) should be classified based on the extent of ventilatory support they are receiving as reflected by $\overline{P}_{aw}$. Our results indicate that a significant percentage of patients (ie, 50%) who are classified as having moderate ARDS using the oxygenation ratio might in fact have severe ARDS according to the oxygenation factor criteria. Similarly, a significant percentage of patients (ie, 50%) who are classified as having mild ARDS using the oxygenation ratio might have either severe or moderate ARDS using the oxygenation factor. These findings can explain the conflicting results reported in patients classified as having moderate ARDS with an oxygenation ratio of 100–200 mm Hg or having mild ARDS with an oxygenation ratio of 200–300 mm Hg who respond differently to the same form of interventions, such as prone positioning, high PEEP, or recruitment maneuvers.[32-35]

The major limitation of this study is that mortality outcomes are not available to make better connections to mortality for the 2 indices; without correlation to mortality, it will be difficult to interpret the clinical importance of having a different severity classification using the oxygenation factor. However, our study was not designed to follow patients until the end of their medical stay, whether in the ICU or the hospital, which is why mortality data is not available. Another limitation is that subjects were identified and included in the study within hours of being in respiratory distress or failure and receiving mechanical ventilation, and they exited the study immediately after initial data collection. Furthermore, it is only logical to establish the utility of the new index, oxygenation factor, before conducting studies that consider mortality as the main outcome. Needless to say, future studies using the new index focusing on mortality as the main outcome are needed. Finally, this study enrolled only subjects who were intubated and receiving invasive mechanical ventilation. However, with the widespread availability and advancements in noninvasive ventilation and high-flow nasal cannula oxygen therapy, many patients with mild or moderate ARDS can be managed with these modalities. Subsequently, the use of the oxygenation factor will be limited in these patients due to the inability to determine $\overline{P}_{aw}$ during noninvasive ventilation and high-flow nasal cannula oxygen therapy.

Conclusions

Our findings suggest that the oxygenation factor that normalizes the oxygen ratio with $\overline{P}_{aw}$ (ie, oxygenation factor = oxygenation ratio/$\overline{P}_{aw}$ = $P_{aO_2}/(F_{IO_2} \times \overline{P}_{aw})$ might be a superior index to use in patients with ARDS, particularly when assessing the oxygenation status and the classifying the severity of ARDS. Subsequently, the Berlin definition for ARDS, which relies on the P_{aO_2}/F_{IO_2} ratio (and does not consider specific ventilatory support settings except for PEEP $\geq$ 5 cm H_2O) might not provide sufficient precision in classifying ARDS and may need to be revised.

ACKNOWLEDGMENTS

The authors are thankful for the help provided by Mr. Marwan Alawiyeh.

REFERENCES

1. Horovitz JH, Carrico CJ, Shires GT. Pulmonary response to major injury. Arch Surg 1974;108(3):349-355.
2. Feiner JR, Weiskopf RB. Evaluating pulmonary function: an assessment of P_{aO_2}/F_{IO_2}. Crit Care Med 2017;45(1):e40-e48.
3. Villar J, Ambrós A, Soler JA, Martínez D, Ferrando C, Solano R, et al. Age, P_{aO_2}/F_{IO_2}, and plateau pressure score: a proposal for a simple outcome score in patients with the acute respiratory distress syndrome. Crit Care Med 2016;44(7):1361-1369.
4. Chen W, Janz DR, Shaver CM, Bernard GR, Bastarache JA, Ware LB. Clinical characteristics and outcomes are similar in ARDS diagnosed by oxygen saturation/FiO_2 ratio compared with P_{aO_2}/F_{IO_2} ratio. Chest 2015;148(6):1477-1483.
5. Brown SM, Duggal A, Hou PC, Tidswell M, Khan A, Exline M, et al. Nonlinear imputation of P_{aO_2}/F_{IO_2} from S_{pO_2}/F_{IO_2} among mechanically ventilated patients in the ICU: a prospective, observational study. Crit Care Med 2017;45(8):1317-1324.
6. Roncon-Albuquerque R Jr, Ferreira-Coimbra J, Vilares-Morgado R, Figueiredo P, Paiva JA. P_{aO_2}/F_{IO_2} deterioration during stable extracorporeal membrane oxygenation associates with protracted recovery and increased mortality in severe acute respiratory distress syndrome. Ann Thorac Surg 2016;102(6):1878-1885.
7. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA 2012;307(23):2526-2533.
8. Villar J, Pérez-Méndez L, Kacmarek R. The Berlin definition met our needs: no. Intensive Care Med 2016;42(5):648-650.
9. Villar J, Pérez-Méndez L, Blanco J, Añón JM, Blanch L, Belda J, et al. A universal definition of ARDS: the P_{aO_2}/F_{IO_2} ratio under a standard ventilatory setting. A prospective, multicenter validation study. Intensive Care Med 2013;39(4):583-592.
10. Villar J, Blanco J, del Campo R, Andaluz-Ojeda D, Díaz-Domínguez FJ, Muriel A, et al. Assessment of P_{aO_2}/F_{IO_2} for stratification of patients with moderate and severe acute respiratory distress syndrome. BMJ Open 2015;5(3):e006812.
11. Hernu R, Wallet F, Thiollière F, Martin O, Richard JC, Schmitt Z, et al. An attempt to validate the modification of the American-European consensus definition of acute lung injury/acute respiratory distress syndrome by the Berlin definition in a university hospital. Intensive Care Med 2013;39(12):2161-2170.
12. Thille AW, Esteban A, Fernández-Segoviano P, Rodriguez JM, Aramburu JA, Peñuelas O, et al. Comparison of the Berlin definition for acute respiratory distress syndrome with autopsy. Am J Respir Crit Care Med 2013;187(7):761-767.
13. Alhurani RE, Oeckler RA, Franco PM, Jenkins SM, Gajic O, Pannu SR. Refractory hypoxemia and use of rescue strategies: a U.S. national survey of adult intensivists. Ann Am Thorac Soc 2016;13(7):1105-1114.
14. El-Khatib MF, Jamaleddine GW. A new oxygenation index for reflecting intrapulmonary shunting in patients undergoing open heart surgery. Chest 2004;125(2):592-596.
15. Primiano FP Jr, Chatburn RL, Lough MD. Mean airway pressure: theoretical considerations. Crit Care Med 1982;10(6):378-383.
16. Bellani G, Grassi A, Sosio S, Gatti S, Kavanagh BP, Pesenti A, Foti G. Driving pressure is associated with outcome during assisted ventilation in acute respiratory distress syndrome. Anesthesiology 2019;131(3):594-604.
17. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015;372(8):747-755.
18. Serpa Neto A, Deliberato RO, Johnson AEW, Bos LD, Amorim P, Pereira SM, et al. Mechanical power of ventilation is associated with mortality in critically ill patients: an analysis of patients in two observational cohorts. Intensive Care Med 2018;44(11):1914-1922.
19. Gattinoni L, Tonetti T, Cressoni M, Cadringher P, Herrmann P, Moerer O, et al. Ventilator related causes of lung injury: the mechanical power. Intensive Care Med 2016;42(10):1567-1575.
20. Becher T, van der Staay M, Schädler D, Frerichs I, Weiler N. Calculation of mechanical power for pressure controlled ventilation. Intensive Care Med 2019;45(9):1321-1323.
21. Chatburn RL, El-Khatib M, Mireles-Cabodevila E. A taxonomy for mechanical ventilation: 10 fundamental maxims. Respir Care 2014;59(11):1747-1763.
22. Villar J, Pérez-Méndez L, Kacmarek RM. Current definitions of acute lung injury and the acute respiratory distress syndrome do not reflect their true severity and outcome. Intensive Care Med 1999;25(9):930-935.
23. Villar J, Pérez-Méndez L, López J, Belda J, Blanco J, Saralegui I, et al. An early PEEP/FIO_2 trial identifies different degrees of lung injury in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2007;176(8):795-804.
24. Valta P, Corbeil C, Chassé M, Braidy J, Milic-Emili J. Mean airway pressure as an index of mean alveolar pressure. Am J Respir Crit Care Med 1996;153(6):1825-1830.
25. Chikhani M, Das A, Haque M, Wang W, Bates DG, Hardman JG. High PEEP in acute respiratory distress syndrome: quantitative evaluation between improved arterial oxygenation and decreased oxygen delivery. Br J Anaesth 2016;117(5):650-658.
26. Wang SH, Wei TS. The outcome of early pressure-controlled inverse ratio ventilation on patients with severe acute respiratory distress syndrome in surgical intensive care unit. Am J Surg 2002;183(2):151-155.
27. Tonetti T, Vasques F, Rapetti F, Maiolo G, Collino F, Romitti F, et al. Driving pressure and mechanical power: new targets for VILI prevention. Ann Transl Med 2017;5(14):286.
28. Toufen Junior C, De Santis Santiago RR, Hirota AS, Carvalho ARS, Gomes S, Amato MBP, Carvalho C. Driving pressure and long-term outcomes in moderate/severe acute respiratory distress syndrome. Ann Intensive Care 2018;8(1):119-128.
29. Parhar KKS, Zjadewicz K, Soo A, Sutton A, Zjadewicz M, Doig L, et al. Epidemiology, mechanical power, and 3-year outcomes in acute respiratory distress syndrome patients using standardized screening: an observational cohort study. Ann Am Thorac Soc 2019;16(10):1263-1272.

30. Gattinoni L, Marini JJ, Collino F, Maiolo G, Rapetti F, Tonetti T, et al. The future of mechanical ventilation: lessons from the present and the past. Crit Care 2017;21(1):183-193.
31. Marini JJ. Evolving concepts for safer ventilation. Crit Care 2019;23 (Suppl 1):114-120.
32. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368(23):2159-2168.
33. Santa Cruz R, Rojas JI, Nervi R, Heredia R, Ciapponi A. High versus low positive end-expiratory pressure (PEEP) levels for mechanically ventilated adult patients with acute lung injury and acute respiratory distress syndrome. Cochrane Database Syst Rev 2013;6:CD009098.
34. Cavalcanti AB, Suzumura ÉA, Laranjeira LN, Paisani DM, Damiani LP, Guimarães HP, et al. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA 2017;318 (14):1335-1345.
35. Bein T, Weber-Carstens S, Goldmann A, Müller T, Staudinger T, Brederlau J, et al. Lower tidal volume strategy (≈3 mL/kg) combined with extracorporeal CO_2 removal versus conventional protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. Intensive Care Med 2013;39(5):847-856.