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Optimizing Patient Care

Making sense of the pressure of arterial oxygen to fractional inspired oxygen concentration ratio in patients with acute respiratory distress syndrome

AF Broccard*

Abstract

Introduction

The pressure of arterial oxygen to fractional inspired oxygen concentration (PaO_2/FIO_2) ratio is a commonly used indicator of lung function in critically ill patients. For many years, physicians have relied on it to define and characterise the severity of the acute respiratory distress syndrome (ARDS), and this ratio is still a central element of the new ARDS definition (Berlin definition). In addition, clinicians utilise this ratio to track change in lung conditions, to set positive end expiratory pressure, to assess the response to different ventilatory strategies and/or to make decisions regarding the requirement for advanced supportive treatment modalities (e.g., paralysis, prone position, extracorporeal membrane oxygenation). Despite having the merit of simplicity and availability, the PaO_2/FIO_2 is more complex to interpret than being acknowledged and can at times be misleading. This risk is particularly present if one does not understand or consider the key determinants of the PaO_2/FIO_2 ratio in each individual patient and why this ratio may change over time. We review here the main determinants of PaO_2/FIO_2 ratio and discuss how the application of a few physiological key concepts can be used to optimise the management of patients with hypoxic respiratory failure.

Conclusion

We need a more individualised approach of hypoxic respiratory failure and ARDS. It is questionable that the new Berlin ARDS definition was the most required change to our approach of ARDS. One could argue that our patients could be better off, if we had moved away from trying to find commonality between very different conditions as the old and new ARDS definitions do. The 'one size fits all' approach tried for many years has not led to substantial progress. It may be high time for a different strategy and during the mean time, it may also be wise to use physiology as a compass to avoid the obvious mistakes associated with a cookbook approach.

* Corresponding author
Email: brocc001@umn.edu

Division of Pulmonary, Allergy, Critical Care and Sleep Medicine Division of the Department of Medicine, University of Minnesota, Minneapolis, MN, U.S.A.

Introduction

In the absence of a direct reliable marker of lung injury, gas exchange is commonly used to define respiratory failure (e.g., hypoxic versus hypercapnic), as well as the degree of lung dysfunction/injury (e.g., mild to severe acute respiratory distress syndrome [ARDS]). For hypoxic respiratory failure, in general and ARDS in particular, the pressure of arterial oxygen to fractional inspired oxygen concentration (PaO_2/FIO_2) ratio is the most commonly reported index of gas exchange impairment and is a central element of the ARDS definition[1]. The recent revised definition (the so-called Berlin definition) has not changed its importance as the PaO_2/FIO_2 ratio is still required to define ARDS and to characterise its severity (mild, moderate or severe)[2]. This ratio is also used to identify the ARDS population, who is the most likely to benefit from specific supportive modalities, such as prone positioning or paralysis. Finally, this ratio is also commonly calculated at the bedside to track the course of ARDS or the response to specific intervention, and to help set positive end expiratory pressure (PEEP) level in individual patients.

Despite its simplicity and availability, the PaO_2/FIO_2 ratio can be complex to interpret and misleading at the bedside if one does not understand or consider its various physiological determinants. We review here the key determinants of PaO_2/FIO_2 ratio and we propose an approach aiming at understanding its meaning in specific patients. We believe that this is important to optimise the management of patients with ARDS.

Discussion

The pressure of arterial oxygen to fractional inspired oxygen concentration and the acute respiratory distress syndrome definition

A detailed discussion of the Berlin definition of ARDS is beyond the scope of this critical review. However, it is relevant to stress the fact that the new ARDS definition mandates this ratio to be less than 300[2]. In addition, the assessment of ARDS severity relies entirely on this ratio (≤300 and >200 mild ARDS, ≤200 and >100 moderate ARDS, ≤100 severe ARDS) measured on a PEEP ≥5 cm H_2O. Although the mild, moderate and severe ARDS of the Berlin definition were found to be associated with different mortality (27%; 95% confidence interval [CI], 24%–30%; 32%; 95% CI, 29%–34%; and 45%; 95% CI, 42%–48%, respectively; $p < 0.001$) and with increased median duration of mechanical ventilation in

For citation purposes: *Broccard AF*. Making sense of the pressure of arterial oxygen to fractional inspired oxygen concentration ratio in patients with acute respiratory distress syndrome. OA Critical Care 2013 Jun 01;1(1):9.

Competing interests: none declared. Conflict of Interests: none declared.
All authors contributed to the conception, design, and preparation of the manuscript, as well as read and approved the final manuscript.
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survivors, it is important to emphasise that such association cannot be extrapolated to individual patients. In addition, the definition lacks standardisation in regard to the key determinants of PaO_2/FIO_2, such as the FIO_2 and PEEP used to measure PaO_2[3]. This is problematic for reasons discussed below.

Determinant of the pressure of arterial oxygen to fractional inspired oxygen concentration ratio in patients with acute respiratory distress syndrome

To appreciate the limitation of applying this ratio to characterise the degree of lung injury in a given patient and to understand that sometimes this ratio changes overtime irrespective of the degree of lung injury, it is important to review the key clinical factors that determine the PaO_2/FIO_2 ratio in the critically ill patients (see Table 1).

In a healthy individual, the main determinant of the PaO_2 is the alveolar O_2 content (PAO_2). When the ventilation to perfusion (V/Q) ratio is close to 1 and therefore only a negligible shunt (perfusion of non-ventilated lung units) is present, the venous blood becomes fully oxygenated and largely independent of the mixed venous O_2 content as the PaO_2 becomes identical to the PAO_2. One of the hallmarks of ARDS is the presence of shunt[4]. Shunt and venous admixtures are used here interchangeably to express the calculated fraction of the cardiac output that bypasses the alveolar units and that contributes to the mixing of the poorly oxygenated venous blood, with the capillary oxygenated one. In contrast to the PaO_2 of the healthy individuals, the one of ARDS patients varies significantly with the degree of V/Q mismatch and/or shunt present and the mixed venous blood O_2 content. As the shunt increases, the PaO_2 tends to become less and less sensitive to the PAO_2 and to the FIO_2 and more and more dependent on the mixed venous O_2 content and saturation. This is due to the fact that the arterial and venous O_2 blood content and saturation tend to become more and more alike as the shunt fraction increases (Figure 1).

The degree of shunt can be viewed as determined and modulated by factors that affect the number of alveolar units that are non-ventilated (V factors) and/or the perfusion of those units (Q factors), as we shall now discuss.

Ventilation (V) factors

In patients with ARDS, non-aerated alveolar units contributing to shunt physiology are mainly the result of alveolar flooding (by oedema, pus or blood) or collapse. Although some units can be easily recruited (e.g., collapsed alveoli) by increasing the transpulmonary pressure, others resist recruitment[5] (e.g., alveoli are filled with pus in the setting of a pneumonia). As a result, the degree of recruitable lung units varies among patients with ARDS[6] and within the same patient over the course of the disease (more recruitable lung early and less later on).

This has important implications. Firstly, depending on the ventilatory strategy used and the degree of recruitable lung at hand, the PaO_2/FIO_2 ratio may vary greatly. This is well illustrated by the study of

Table 1 Key determinant of the PaO_2/FIO_2 in patients with ARDS.

PaO_2/FIO_2 ratio determinants	Corresponding primary modulating factors	Corresponding secondary modulating factors	Common mechanisms
PaO_2	Alveolar PO_2	FIO_2	Change in FIO_2
	Shunt	V factors	Size of the 'baby' lung, recruitability and ventilatory strategy (e.g., PEEP)
		Q factors	Hypoxia vasoconstriction, airway pressure, position
	Mixed venous O_2 content	O_2 delivery	Reduced cardiac output, reduced hemoglobin, reduced O_2 saturation
		O_2 consumption	Increased O_2 extraction
FIO_2	Target PaO_2	Physician dependent	
PaO_2/FIO_2	FIO_2	The effect of the FIO_2 on this ratio is quite variable depending for instance on the degree of shunt (change in opposite direction)	Arterio-venous difference or Change in degree of shunt

ARDS, acute respiratory distress syndrome; PEEP, positive end expiratory pressure.

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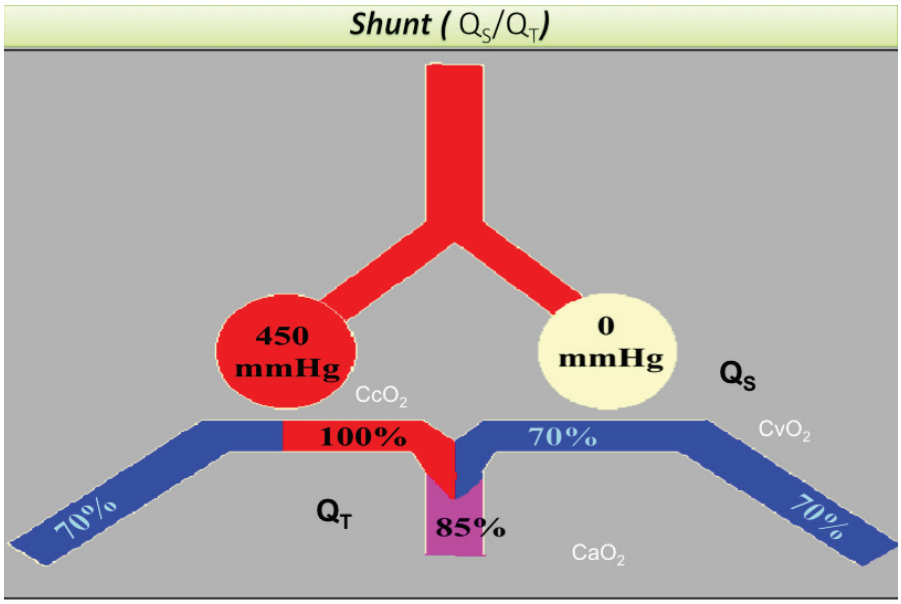

Figure 1: Shunt physiology.
The oxygen content and saturation of the total lung blood flow (Q_T) is a function of the amount of blood flow that bypasses aerated alveoli (venous admixture or Q_S). QS/QT represents the degree of shunt. The arterial blood oxygen blood content is the product of the mixing of oxygenated blood (Q_T–Q_S) and venous blood (Q_S). When shunt is present, arterial blood O_2 content CaO_2 = [Hb (gm/dL) × 1.34 mL O_2/gm Hb × Sat O_2 + PaO_2 × (0.003 ml O_2/mm Hg/dL)] = Q_S/Q_T * CvO_2 + (Q_T–Q_S)/Q_T × CcO_2. This can be simplified by substituting oxygen content (C × O_2) by O_2 saturation where x = a for arterial, c for capillary or v for venous blood. For a 50% shunt and a mixed venous O_2 saturation of 70% percent, the calculated arterial O_2 saturation is 85%. Note that a drop in SvO_2 to 60% would reduce the SaO_2 to 80%. An effective hypoxic vasoconstriction that reduces the shunt fraction to 20% would bring it back up to arterial saturation to 92.5%.

Grasso et al. performed in ARDS patients[5]. In patients with no significant recruitable lung (non-recruiter), higher PEEP had no effect on the PaO_2/FIO_2 ratio. In recruiters in contrast, PEEP often causes this ratio to increase leading to a downgrade in ARDS severity. In addition, other patients may not meet the ARDS definition any more (ratio above 300 on high PEEP). Secondly, the presence of distinct ARDS populations (recruiters and non-recruiters), undermines and discredits the use of FIO_2 tables proposed by some to set the PEEP level[7]. Indeed, in patients with a similar large shunt, but with a marked difference in the amount of recruitable lung (and therefore, response to PEEP), such tables would lead physicians to choose a high PEEP (persistent high FIO_2 requirement) in the non–recruiters, who are the least likely to benefit from PEEP. Comparatively, such tables lead to choose a lower PEEP in the recruiters than in the non-recruiters, given that the response to PEEP allows reducing the FIO_2. Everything else being equal, setting the PEEP based on such table puts the non-recruitable patients at risk of volutrauma (high PEEP no recruitment), and the recruitable patients at risk for atelectrauma from tidal opening and collapse (PEEP level too low to prevent cyclical alveolar collapse)[8,9]. We believe that such tables[7] lack sound physiological rationale, validation and should thus, not be used to guide the choice of PEEP.

It is also worth mentioning that in the first ARDS net trial, which compared low versus high tidal volume, the strategy associated with the highest PaO_2/FIO_2 ratio at the onset of the study, was the high-tidal volume approach[7]. The latter was associated with the worse outcome. It is thus, important not to infer from the ARDS severity definition that the best strategy can be identified by simply looking at its impact on the PaO_2/FIO_2 ratio, which does not appear to be a reliable outcome surrogate.

As a final word, venous admixture correlates with the non-inflated tissue mass and lung compliance, with the size of the normally aerated lung or 'baby lung'[10]. Any obvious discrepancy between the extent of lung infiltrates and/or respiratory mechanics on one end and the degree of venous admixture (e.g., severe shunt, with unexpected low amount of infiltrates and/or essentially unaltered respiratory system compliance) should raise the possibility that other factors might be contributing to low arterial oxygen content, as we shall now discuss.

Perfusion factors

In addition to taking into account the number of alveolar units not contributing to gas exchange, one also has to consider the factors that regulate their perfusion. The reduced blood flow through non-aerated alveoli in response to alveolar hypoxia can vary significantly because of the presence or absence of factors, which have the potential to either enhance or blunt the hypoxic vasoconstriction response. For instance, sepsis[11], alkalemia[12], a high cardiac output during positive pressure ventilation (but not during spontaneous breathing or medications, such as intravenous vasodilators) tend to blunt the hypoxic response and increase the degree of venous admixture[13]. In contrast, inhaled vasodilators[14] or positioning with the good lung down or prone help to

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redistribute blood flow to the aerated lung and thus, to reduce venous admixture[15]. Finally, the application of excessive airway pressure on an aerated compliant lung (when the other one is extensively consolidated and non-compliant) results in alveolar vessel compression in the good lung, in redistribution of blood flow to the bad one and in increasing shunt. The wide range of correlations reported (r = 0.5–0.9) between the PaO_2/FIO_2 ratio and degree of shunt[16] points toward PaO_2/FIO_2 ratio modulator factors other than shunt alone, as we shall now discuss.

Extra pulmonary factors: mixed venous oxygen content, cardiac output and cardiac shunt

As discussed above, mixed venous O_2 content together with the percentage of cardiac output that bypasses aerated lung units (venous admixture) are key determinants of the PaO_2, arterial O_2 saturation and content in patients with ARDS (see Figure 1). As the mixed venous O_2 content and saturation decrease, so does the arterial PaO_2 in the setting of shunt physiology. It follows that any primary increase in tissue consumption (VO_2) or reduction in tissue oxygen delivery (DO_2) associated with a compensatory increased in O_2 extraction may cause a drop in the mixed venous PO_2, O_2 content and saturation and therefore, in the PaO_2. This effect is trivial for a small pulmonary shunt, but significant for a large one. In ADRS patients, a drop in cardiac output is not an uncommon cause of decreased PaO_2. This should be suspected in all patients, who developed a drop in O_2 saturation, with unchanged respiratory system mechanics, particularly if it is associated with hypotension. The effect of an increase in CO on the mixed venous O_2 is more complex as the resulting increase in the mixed venous PO_2, saturation and O_2 content may be offset by the greater shunt associated with the higher CO[17].

It is important to consider the cardiac output and the relationship between O_2 delivery and demand as a potential cause of a change in PaO_2 in ARDS. For instance, if a patient meets severe ARDS criteria mainly due to a low CO and reduced mixed venous O_2 saturation as opposed to a large shunt, the priority would be to restore an adequate haemodynamic and not to embark on recruitment manoeuvres or extracorporeal membrane oxygenation. Not distinguishing the different mechanisms and the cause for reaching a PaO_2/FIO_2 less than 100 may thus, lead to very inappropriate intervention (increasing the PEEP in a patient with low CO due to decompensated cor pulmonale). It is also worth remembering that cor pulmonale (which has been reported to be present in approximately 25% of ARDS patients[18]) should be systematically searched for in this setting.

Finally, it is also important to remember that approximately 15% of patients with ARDS may also have a cardiac shunt from right to left through a patent foramen ovale[19]. An echocardiogram with a bubble study should thus be obtained whenever a low PaO_2/FIO_2 ratio cannot be clearly explained by the extent of the non-aerated alveolar process alone, a low-mixed venous O_2 saturation or circumstances known to be associated with impaired hypoxic vasoconstriction. Worsening gas exchange when PEEP is dialled up not only can be an important clue to the presence of a right to left shunt through a patent foramen ovale, but also can be seen in the presence of a decompensated cor pulmonale or hypovolemia. Those three possibilities are usually easy to differentiate from each other by a bedside echocardiogram.

Physicians and fractional inspired oxygen factors

Unintended physicians' contributions to the PaO_2/FIO_2 ratio are often under-appreciated. This is the consequence of variable practice and recommendation regarding which PaO_2 to target in ARDS. In the ARDS net trials[20], the explicit targets were 55–80 mm Hg for the PaO_2 and 88–95 for the arterial O_2 saturation. Let us consider the implication of those targets in a patient with a 30% shunt. If one targets a PaO_2 of 60 mm Hg, the FIO_2 required to achieve that target would be 0.5 and the corresponding PaO_2/FIO_2 would be 120 (moderate ARDS). If one targets a PaO_2 of 80 mm Hg, the required FIO_2 would be 1 and the resulting PaO_2/FIO_2 would be 80 (severe ARDS). In other words, depending on the targeted PaO_2, the apparent ARDS severity may changed.

Finally, it is important to stress that varying the FIO_2 has different effects on the PaO_2/FIO_2 ratio depending on the degree of intrapulmonary shunt, arterio-venous differences, $PaCO_2$, respiratory quotient and haemoglobin under conditions of constant metabolism and ventilation/perfusion abnormality[21]. For instance, increasing the FIO_2 causes the PaO_2/FIO_2 ratio to rise if intrapulmonary shunt is small, but to drop if the shunt is large (Figure 2, panel B).

Conclusion

As implied by the ARDS definition, the PaO_2/FIO_2 ratio should ideally closely reflect the degree of lung injury and extent of alveolar flooding/collapse. Although there is clearly an association between this ratio and ARDS severity at least when the definition is applied to a population, the reality at the bedside is more complex, particularly if this ratio is calculated without standardising the levels of FIO_2 (e.g., measurement at an FIO_2 of 1 avoid the problem of the variable impact of the FIO_2 on the ratio) and of PEEP, given that some patients are recruiters and others are not.

As discussed above, the PaO_2/FIO_2 ratio does not linearly track the degree of lung injury (severity) and may change for reasons that are completely independent of the lungs (e.g., a change in CO and mixed

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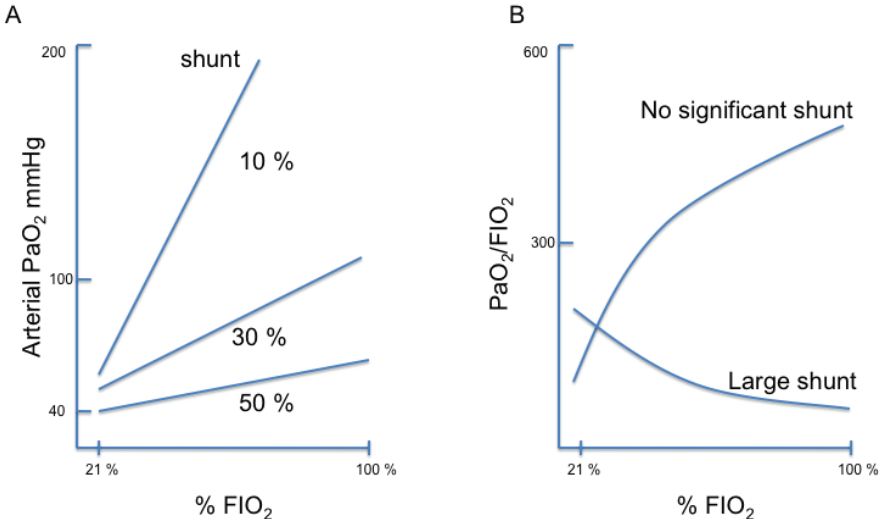

Figure 2: Relationships between PaO_2, FIO_2 and shunt.
Panel A shows the relationships between FIO_2 and PaO_2 for different degrees of shunts. Notice that increasing the FIO_2 has less and less effect on the PaO_2, as the degree of shunt increases.
Panel B shows that the relationship between FIO_2 and PaO_2/FIO_2 varies with the degree of shunt. This is explained by the relationship demonstrated in Panel A.

Table 2 Clues to the underlying cause(s) for a change in the PaO_2/FIO_2 ratio in a patient with ARDS.

Possible clues	Mechanisms	Examples
Change in respiratory system mechanics or X-ray	Change in alveolar units ventilation: V factors	Increased infiltrates, edema, atelectasis, pneumothorax
Vasoactive medication started or stopped or Presence of a condition affecting the hypoxic vasoconstriction or the regional distribution of perfusion and Unchanged X-ray, respiratory mechanic or hemodynamics	Change in the perfusion of ventilated and non aerated alveolar units: Q factors	IV Vasodilator started Change in position, acid-base status
Different providers caring for a patient	Different ventilator strategies	Change in FIO_2, PEEP, or Vt
Hypotension, cor pulmonale on echo, low cardiac output or mixed venous O_2 saturation	Increased O_2 extraction	Anemia, cor pulmonale

ARDS, acute respiratory distress syndrome; IV, intravenous; PEEP, positive end expiratory pressure; Vt, tidal volume.

venous O_2). Simply turning up the FIO_2 or PEEP knob when PaO_2/FIO_2 decreases and assuming that in every patient this ratio more or less linearly reflects ARDS severity is a potentially armful approach.

Interpreting this ratio at the bedside is not that simple and requires a good understanding of cardiopulmonary physiology, a sound clinical judgment and a thoughtful approach (see Table 2). A correct interpretation may require obtaining and/or reviewing the following data: 1. an arterial and venous blood gas to confirm the pulse oximetry reading and assess the venous O_2 saturation 2. recent ventilator setting changes particularly to PEEP, FIO_2 and tidal volume 3. the chest X-ray or computed tomography and respiratory mechanic measurements to assess the alveolar flooding or collapse and the size of the 'baby lung' (to look for unaccounted discrepancy between those parameters and the degree of shunt present) 4. a haemodynamic/cardiac evaluation by performing a point-of-care ultrasound to assess for the presence of cor pulmonale and cardiac shunt 5. the conditions that have the potential to affect hypoxic vasoconstriction.

We need a more individualised approach of hypoxic respiratory failure and ARDS. It is questionable that the new Berlin ARDS definition was the most required change to our approach of ARDS. One could argue that our patients could be better off, if we had moved away from trying to find commonality between very different conditions as the old and new ARDS definitions do. The 'one size fits all' approach tried for many years has not led to substantial progresses. It may be high time for a different strategy and during the mean time, it may also be wise to use physiology as a compass to avoid the obvious mistakes associated with a cookbook approach.

Abbreviations list

ARDS, acute respiratory distress syndrome; PaO_2/FIO_2, pressure of arterial oxygen to fractional inspired oxygen concentration; PEEP, positive end expiratory pressure; V/Q, ventilation to perfusion.

Competing interests: none declared. Conflict of Interests: none declared.
All authors contributed to the conception, design, and preparation of the manuscript, as well as read and approved the final manuscript.
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