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

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Abstract

Introduction

The pressure of arterial oxygen to fractional inspired oxygen concentration (PaO2/FIO2) 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 PaO2/FIO2 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 various 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.

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 (PaO2/FIO2) ratio is the most commonly reported index of gas exchange impairment and is a central element of the ARDS definition. The recent revised definition (the so-called Berlin definition) has not changed its importance as the PaO2/FIO2 ratio is still required to define ARDS and to characterise its severity (mild, moderate or severe). 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 PaO2/FIO2 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 PaO2/FIO2 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 3002. 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 H2O. 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...
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 PaO2/FIO2, such as the FIO2 and PEEP used to measure PaO2. 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 PaO2/FIO2 ratio in the critically ill patients (see Table 1).

In a healthy individual, the main determinant of the PaO2 is the alveolar O2 content (PAO2). 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 O2 content as the PaO2 becomes identical to the PAO2. One of the hallmarks of ARDS is the presence of shunt4. 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 PaO2 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 O2 content. As the shunt increases, the PaO2 tends to become less and less sensitive to the PAO2 and to the FIO2 and more and more dependent on the mixed venous O2 content and saturation. This is due to the fact that the arterial and venous O2 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 recruitment2 (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 ARDS3 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 PaO2/FIO2 ratio may vary greatly. This is well illustrated by the study of

| Table 1 Key determinant of the PaO2/FIO2 in patients with ARDS. |
|----------------|-----------------------------|-------------------------------|
| PaO2/FIO2 ratio determinants | Corresponding primary modulating factors | Corresponding secondary modulating factors | Common mechanisms |
| PaO2 | Alveolar PO2 | FIO2 | Change in FIO2 |
| Shunt | V factors | Size of the ‘baby’ lung, recruitability and ventilatory strategy (e.g., PEEP) |
| Q factors | Hypoxia vasoconstriction, airway pressure, position |
| Mixed venous O2 content | O2 delivery | Reduced cardiac output, reduced hemoglobin, reduced O2 saturation |
| O2 consumption | Increased O2 extraction |
| FIO2 | Target PaO2 | Physician dependent |
| PaO2/FIO2 | FIO2 | The effect of the FIO2 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 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 $CaO_2 = [Hb (gm/dL) \times 1.34 \text{ mL O}_2/\text{gm Hb} \times \text{Sat } O_2 + \text{PaO}_2 \times (0.003 \text{ ml O}_2/\text{mm Hg} \text{ Hg/dL})] = Q_s/QT \times CcO_2 + (Q_T-Q_s)/QT \times CvO_2$. This can be simplified by substituting oxygen content ($C \times x$) 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. 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. 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). We believe that such tables’ 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. 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”. 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, alkalemia, 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. In contrast, inhaled vasodilators or positioning with the good lung down or prone help to...
redistribute blood flow to the aerated lung and thus, to reduce venous admixture. 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 PaO2/FIO2 ratio and degree of shunt points toward PaO2/FIO2 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 O2 content together with the percentage of cardiac output that bypasses aerated lung units (venous admixture) are key determinants of the PaO2, arterial O2 saturation and admixture) are key determinants of bypasses aerated lung units (venous admixture) are key determinants of the PaO2, arterial O2 saturation and admixture). Not distinguishing the different mechanisms and the cause for reaching a PaO2/FIO2 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) 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. An echocardiogram with a bubble study should thus be obtained whenever a low PaO2/FIO2 ratio cannot be clearly explained by the extent of the non-aerated alveolar process alone, a low-mixed venous O2 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 PaO2/FIO2 ratio are often under-appreciated. This is the consequence of variable practice and recommendation regarding which PaO2 to target in ARDS. In the ARDS net trials, the explicit targets were 55–80 mm Hg for the PaO2 and 88–95 for the arterial O2 saturation. Let us consider the implication of those targets in a patient with a 30% shunt. If one targets a PaO2 of 60 mm Hg, the FIO2 required to achieve that target would be 0.5 and the corresponding PaO2/FIO2 would be 120 (moderate ARDS). If one targets a PaO2 of 80 mm Hg, the required FIO2 would be 1 and the resulting PaO2/FIO2 would be 80 (severe ARDS). In other words, depending on the targeted PaO2 the apparent ARDS severity may changed.

Finally, it is important to stress that varying the FIO2 has different effects on the PaO2/FIO2 ratio depending on the degree of intrapulmonary shunt, arterio-venous differences, PaCO2 respiratory quotient and haemoglobin under conditions of constant metabolism and ventilation/perfusion abnormality. For instance, increasing the FIO2 causes the PaO2/FIO2 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 PaO2/FIO2 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 FIO2 (e.g., measurement at an FIO2 of 1 avoid the problem of the variable impact of the FIO2 on the ratio) and of PEEP, given that some patients are recruiters and others are not.

As discussed above, the PaO2/FIO2 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...
Interpreting this ratio at the bedside is not that simple and requires a good understanding of cardiorespiratory physiology, 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 O₂ saturation; 2. recent ventilator setting changes particularly to PEEP, FIO₂ 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. 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 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.

### Abbreviations list

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

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References

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