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EDITORIAL

Benefits and risks of the P/F approach

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Introduction

The PaO_2/FIO_2 ratio represents the pressure exerted in the blood by the unbound molecules of oxygen, normalized to the fractional volume of inspired oxygen. The PaO_2/FIO_2 ratio is used to assess the lung's capability to oxygenate the blood, primarily in ARDS, where its thresholds of 150, 200, and 300 are used/proposed to classify ARDS severity [1, 2]. Ideally, a given PaO_2/FIO_2 ratio value should correspond to a definite lung severity, independently of FIO_2. In reality, the same severity may be associated with quite different PaO_2/FIO_2 values, depending on several factors, as previously described [3].

Alveolar PO_2

Ideally, PaO_2 should be normalized to alveolar PO_2 (PAO_2) instead of FIO_2. Indeed, for the same PaO_2/FIO_2 ratio, the PaO_2/PAO_2 ratio may vary depending on barometric pressure (Pb), $PaCO_2$, and the respiratory exchange ratio (R), as may be easily understood by examining the alveolar air equation:

$$PAO_2 = FIO_2 \times (Pb - 47) - \frac{PaCO_2}{R} \tag{1}$$

Consequently, an identical PaO_2/FIO_2 ratio of 150 measured at the barometric pressure of Mexico City (2250 m) or Göttingen (150 m) in two patients breathing 30% O_2, with identical $PaCO_2/R$ ratios, would result in a sharply different PaO_2/PAO_2 ratios: 0.32 in Göttingen, decidedly less than the 0.49 in Mexico. The impact of $PaCO_2/R$ ratio on PAO_2 is less dramatic, unless extracorporeal CO_2 removal is in use. In this case, the R may be very low, producing a consistent decrease in the alveolar PO_2, if FIO_2 is not adequately increased [4–6].

Arterial PO_2

According to Riley's model (two compartment lung, one ideally perfused and ventilated, one perfused and not ventilated) [7], the arterial oxygen content (CaO_2) is the weighted mean of the oxygen contents blended from the two compartments. The blood from the perfused/ventilated compartment will have a PO_2 equal to the alveolar PAO_2 in equilibrium with the capillary oxygen content (CcO_2), while the blood coming from the perfused/non-ventilated compartment will have a PO_2 and oxygen content equal to the mixed venous blood (CvO_2). The fraction of the cardiac output coming from the perfused/non-ventilated compartment (venous admixture) may be easily quantitated at the bedside:

$$\text{Venous admixture} = \frac{CcO_2 - CaO_2}{CcO_2 - CvO_2}. \tag{2}$$

Although venous admixture is the variable that more accurately assesses oxygenation impairment, it nowadays is considered impractical and cumbersome; hence, the PaO_2/FIO_2 is used for severity assessment. The limits of the PaO_2/FIO_2 approach can be understood by considering Eq. 1 (which defines the PAO_2) together with Eq. 2 (which defines the venous admixture). Indeed,

1. CcO_2 strictly depends on PAO_2, which is proportional to the FIO_2 (Eq. 1), while the CaO_2 is proportional to the PaO_2 (through the oxygen dissociation curve) [8]. Therefore, the difference ($CcO_2 - CaO_2$) and the ratio (CaO_2/CcO_2) are strictly related and hold the same physiological meaning of PaO_2/FIO_2 ratio.
2. Because the ($CcO_2 - CaO_2$) difference equals the product: [venous admixture × ($CcO_2 - CvO_2$)], the same ($CcO_2 - CaO_2$), i.e., the same PaO_2/FIO_2, may derive from myriad combinations of venous admixture fraction and ($CcO_2 - CvO_2$). These range from

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extremely high venous admixture fraction and low ($CcO_2 - CvO_2$), i.e., high CvO_2, or vice versa.

3. CcO_2 primarily depends on FIO_2; therefore, for a given FIO_2 any change of ($CcO_2 - CvO_2$) only depends upon the CvO_2.
4. CvO_2, for a given arterial oxygenation, strictly depends on oxygen consumption (VO_2) and cardiac output (Qt); indeed, $CvO_2 = CaO_2 - VO_2/Qt$.

The consequence of these relationships are summarized in Fig. 1. Figure 1a shows PaO_2 as a function of FIO_2 at venous admixture levels from 10% to 40%, and a cardiac output range between 6 and 10 L/min, assuming an oxygen consumption of 200 ml/min. Two features are worth noting:

- PaO_2 is lower at higher venous admixture levels and increases non-linearly with FIO_2 along the iso-venous admixture lines.
- For a given oxygen consumption and venous admixture level, cardiac output exerts a tremendous effect on PaO_2. It must be stressed, however, that the primary determinant is the CvO_2 (see point 4 above).

Figure 1b presents the PaO_2/FIO_2 ratio as a function of FIO_2 at venous admixture levels between 10% and 40% over a cardiac output range between 6 L/min (lover CvO_2) and 10 L/min (higher CvO_2). This figure underlines the limits of PaO_2/FIO_2 alone in the assessment of lung injury severity. As an example, at venous admixture 20% and 10 L/min of cardiac output, the PaO_2/FIO_2 always exceeds 300, i.e., no ARDS. However, for the same venous admixture (20%) with a lower cardiac output of 6 L/min, a given patient would be classified as "mild ARDS" across FIO_2 values from 0.3 to 0.7 but classified as "no ARDS" at FIO_2 values from 0.7 to 1.0. Another hypothetical patient at venous admixture of 30%, depending on FIO_2 and cardiac output, may oscillate between no ARDS, mild ARDS, or moderate-severe ARDS.

Clinical use

Assessment of severity

Although the PaO_2/FIO_2 ratio has limits as a surrogate of venous admixture, the PaO_2/FIO_2 ratio offers several advantages: first, it is easy to measure; second, when tested across large populations (but not necessarily in individual patients), the PaO_2/FIO_2 reflects reasonably well the severity of anatomical derangements measured by CT scanning [1]. Nonetheless, the accuracy of PaO_2/FIO_2 ratio for indexing ARDS severity (e.g., Berlin ARDS definition) would improve greatly if determined at a standard PEEP value. In previous work [10], we used 5 cmH_2O to avoid the masking effect of higher PEEP on PaO_2/FIO_2 ratio, which may be due either to decreasing venous admixture or altering hemodynamics. Standardization of FIO_2 would further improve the accuracy and comparability of severity among patients [11].

PEEP selection

Changes in PaO_2/FIO_2 ratio are frequently used to assess recruitability during ARDS, on the assumption that increases in PaO_2/FIO_2 ratio are due to lung recruitment [12]. Unfortunately, increasing PEEP often decreases cardiac output. Theoretically, if the venous admixture and

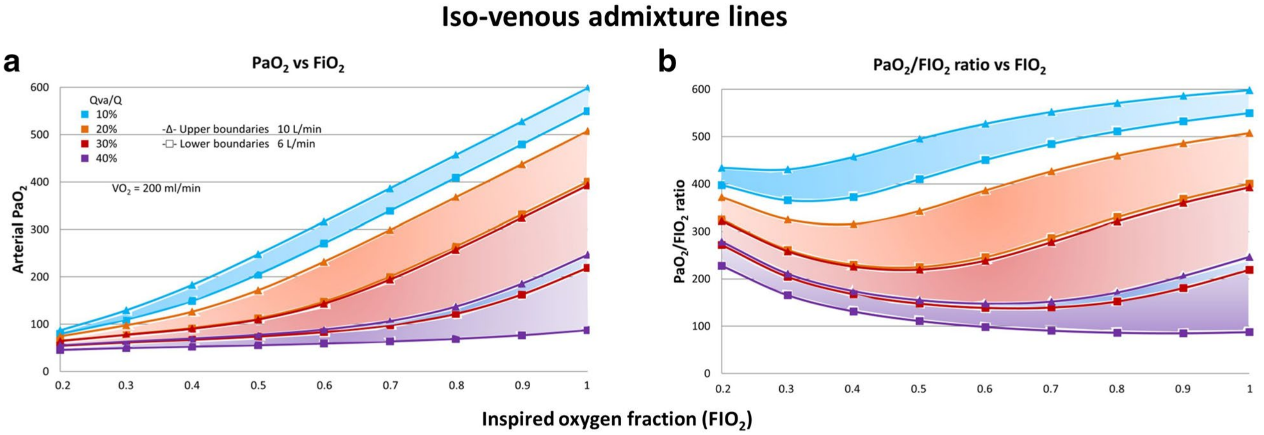

Fig. 1 PaO_2 (**a**) and PaO_2/FIO_2 (**b**) as a function of FIO_2 at shunt of 10%, 20%, 30%, and 40%. Values computed at cardiac output 10 L/min (upper boundaries) and 6 L/min (lower boundaries), at VO_2 200 ml/min, hemoglobin 10 g/dL, and alveolar PCO_2 40 mmHg. PaO_2 values were derived from oxygen content, by using the oxygen dissociation curve equation, proposed by Severinghaus [9]. The arteriovenous oxygen difference was 2 ml/dL at 10 L/min of cardiac output and 3.3 ml/dL at 6 L/min of cardiac output. Note that, for a given shunt, the upper boundary would move up and the lower boundary would move down if the arteriovenous oxygen difference was lower than 2 ml/dL and greater than 3.3 ml/dL, respectively. Values were chosen as proof of the concept

oxygen consumption do not change, this would reduce the PaO_2/FIO_2 ratio. However, this seldom occurs, as the venous admixture usually changes in proportion to the cardiac output [12–15]. Therefore, caution must be used when setting PEEP with the PaO_2/FIO_2 approach, as its apparent that improvement may be due to decreased cardiac output in the absence of recruitment—a principle long known but often forgotten.

Conclusions

- PaO_2/FIO_2 ratio is a surrogate of venous admixture measurement for approximating ARDS severity and relates well to anatomical differences on the CT scan.
- At a given venous admixture, the PaO_2/FIO_2 ratio may differ, depending on oxygen consumption and cardiac output. Conversely, for the same PaO_2/FIO_2, venous admixture may vary with FIO_2.
- To better assess severity of lung injury and follow its evolution, PaO_2/FIO_2 ratio should be measured at standardized levels of PEEP and FIO_2. Selecting PEEP according to PaO_2/FIO_2 ratio may be misleading if hemodynamics are not taken into account.

Compliance with ethical standards

Conflicts of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

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