



# Benefits and risks of the P/F approach

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## Introduction

The  $\text{PaO}_2/\text{FIO}_2$  ratio represents the pressure exerted in the blood by the unbound molecules of oxygen, normalized to the fractional volume of inspired oxygen. The  $\text{PaO}_2/\text{FIO}_2$  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  $\text{PaO}_2/\text{FIO}_2$  ratio value should correspond to a definite lung severity, independently of  $\text{FIO}_2$ . In reality, the same severity may be associated with quite different  $\text{PaO}_2/\text{FIO}_2$  values, depending on several factors, as previously described [3].

## Alveolar $\text{PO}_2$

Ideally,  $\text{PaO}_2$  should be normalized to alveolar  $\text{PO}_2$  ( $\text{PAO}_2$ ) instead of  $\text{FIO}_2$ . Indeed, for the same  $\text{PaO}_2/\text{FIO}_2$  ratio, the  $\text{PaO}_2/\text{PAO}_2$  ratio may vary depending on barometric pressure ( $P_b$ ),  $\text{PaCO}_2$ , and the respiratory exchange ratio ( $R$ ), as may be easily understood by examining the alveolar air equation:

$$\text{PAO}_2 = \text{FIO}_2 \times (P_b - 47) - \frac{\text{PaCO}_2}{R} \quad (1)$$

Consequently, an identical  $\text{PaO}_2/\text{FIO}_2$  ratio of 150 measured at the barometric pressure of Mexico City (2250 m) or Göttingen (150 m) in two patients breathing 30%  $\text{O}_2$ , with identical  $\text{PaCO}_2/R$  ratios, would result in a sharply different  $\text{PaO}_2/\text{PAO}_2$  ratios: 0.32 in Göttingen, decidedly less than the 0.49 in Mexico. The impact of  $\text{PaCO}_2/R$  ratio on  $\text{PAO}_2$  is less dramatic, unless extracorporeal  $\text{CO}_2$  removal is in use. In this case, the  $R$  may be very low, producing a consistent decrease in the alveolar  $\text{PO}_2$ , if  $\text{FIO}_2$  is not adequately increased [4–6].

## Arterial $\text{PO}_2$

According to Riley's model (two compartment lung, one ideally perfused and ventilated, one perfused and not ventilated) [7], the arterial oxygen content ( $\text{CaO}_2$ ) is the weighted mean of the oxygen contents blended from the two compartments. The blood from the perfused/ventilated compartment will have a  $\text{PO}_2$  equal to the alveolar  $\text{PAO}_2$  in equilibrium with the capillary oxygen content ( $\text{CcO}_2$ ), while the blood coming from the perfused/non-ventilated compartment will have a  $\text{PO}_2$  and oxygen content equal to the mixed venous blood ( $\text{CvO}_2$ ). The fraction of the cardiac output coming from the perfused/non-ventilated compartment (venous admixture) may be easily quantitated at the bedside:

$$\text{Venous admixture} = \frac{\text{CcO}_2 - \text{CaO}_2}{\text{CcO}_2 - \text{CvO}_2} \quad (2)$$

Although venous admixture is the variable that more accurately assesses oxygenation impairment, it nowadays is considered impractical and cumbersome; hence, the  $\text{PaO}_2/\text{FIO}_2$  is used for severity assessment. The limits of the  $\text{PaO}_2/\text{FIO}_2$  approach can be understood by considering Eq. 1 (which defines the  $\text{PAO}_2$ ) together with Eq. 2 (which defines the venous admixture). Indeed,

1.  $\text{CcO}_2$  strictly depends on  $\text{PAO}_2$ , which is proportional to the  $\text{FIO}_2$  (Eq. 1), while the  $\text{CaO}_2$  is proportional to the  $\text{PaO}_2$  (through the oxygen dissociation curve) [8]. Therefore, the difference ( $\text{CcO}_2 - \text{CaO}_2$ ) and the ratio ( $\text{CaO}_2/\text{CcO}_2$ ) are strictly related and hold the same physiological meaning of  $\text{PaO}_2/\text{FIO}_2$  ratio.
2. Because the ( $\text{CcO}_2 - \text{CaO}_2$ ) difference equals the product: [venous admixture  $\times$  ( $\text{CcO}_2 - \text{CvO}_2$ )], the same ( $\text{CcO}_2 - \text{CaO}_2$ ), i.e., the same  $\text{PaO}_2/\text{FIO}_2$ , may derive from myriad combinations of venous admixture fraction and ( $\text{CcO}_2 - \text{CvO}_2$ ). 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 (lower  $CvO_2$ ) 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.

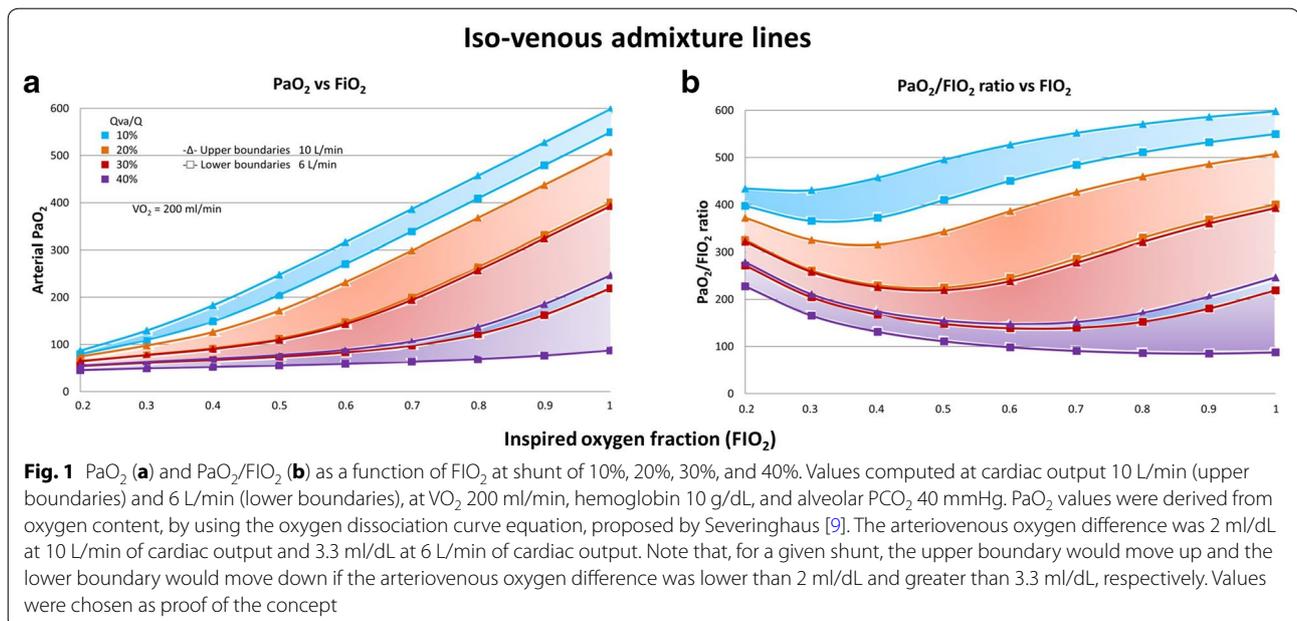
## Clinical use

### 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<sub>2</sub>O 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



oxygen consumption do not change, this would reduce the  $\text{PaO}_2/\text{FIO}_2$  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  $\text{PaO}_2/\text{FIO}_2$  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

- $\text{PaO}_2/\text{FIO}_2$  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  $\text{PaO}_2/\text{FIO}_2$  ratio may differ, depending on oxygen consumption and cardiac output. Conversely, for the same  $\text{PaO}_2/\text{FIO}_2$ , venous admixture may vary with  $\text{FIO}_2$ .
- To better assess severity of lung injury and follow its evolution,  $\text{PaO}_2/\text{FIO}_2$  ratio should be measured at standardized levels of PEEP and  $\text{FIO}_2$ . Selecting PEEP according to  $\text{PaO}_2/\text{FIO}_2$  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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