Introduction

The acute respiratory distress syndrome (ARDS) is characterized by severe hypoxemia, a cornerstone element in its definition. Numerous indices have been used to describe this hypoxemia, such as the arterial to alveolar O\textsubscript{2} difference, the intrapulmonary shunt fraction, the oxygen index and the PaO\textsubscript{2}/F\textsubscript{I}O\textsubscript{2} ratio. Of these different indices the PaO\textsubscript{2}/F\textsubscript{I}O\textsubscript{2} ratio has been adopted for routine use because of its simplicity. This ratio is included in most ARDS definitions, such as the Lung Injury Score [1] and in the American–European Consensus Conference Definition [2]. Ferguson et al. recently proposed a new definition including static respiratory system compliance and PaO\textsubscript{2}/F\textsubscript{I}O\textsubscript{2} measurement with PEEP set above 10 cmH\textsubscript{2}O, but F\textsubscript{I}O\textsubscript{2} was still not fixed [3]. Important for this discussion, the PaO\textsubscript{2}/F\textsubscript{I}O\textsubscript{2} ratio is influenced not only by ventilator settings and PEEP but also by F\textsubscript{I}O\textsubscript{2}. First, changes in F\textsubscript{I}O\textsubscript{2} influence the intrapulmonary shunt fraction, which equals the true shunt plus ventilation–perfusion mismatching. At F\textsubscript{I}O\textsubscript{2} 1.0, the effects of ventilation–perfusion mismatch are eliminated and true intrapulmonary shunt is measured. Thus, the estimated shunt fraction may decrease as F\textsubscript{I}O\textsubscript{2} increases if V/Q mismatch is a major component in inducing hypoxemia (e.g., chronic obstructive lung disease and asthma). Second, at an F\textsubscript{I}O\textsubscript{2} of 1.0 absorption atelectasis may occur, increasing true shunt [4]. Thus, at high F\textsubscript{I}O\textsubscript{2} levels (> 0.6) true shunt may progressively increase but be reversible by recruitment maneuvers. Third, because of the complex mathematical relationship between the oxy-hemoglobin dissociation curve, the arterio-venous O\textsubscript{2} difference, the PaCO\textsubscript{2} level and the hemoglobin level, the relation between PaO\textsubscript{2}/F\textsubscript{I}O\textsubscript{2} ratio and F\textsubscript{I}O\textsubscript{2} is neither constant nor linear, even when shunt remains constant.

Gowda et al. [5] tried to determine the usefulness of indices of hypoxemia in ARDS patients. Using the 50-compartment model of ventilation–perfusion inhomogeneity plus true shunt and dead space, they varied the F\textsubscript{I}O\textsubscript{2} between 0.21 and 1.0. Five indices of O\textsubscript{2} exchange efficiency were calculated (PaO\textsubscript{2}/F\textsubscript{I}O\textsubscript{2}, venous admixture, P(A-a)O\textsubscript{2}, PaO\textsubscript{2}/alveolar PO\textsubscript{2}, and the respiratory index). They described a curvilinear shape of the curve for PaO\textsubscript{2}/F\textsubscript{I}O\textsubscript{2} ratio as a function of F\textsubscript{I}O\textsubscript{2}, but PaO\textsubscript{2}/F\textsubscript{I}O\textsubscript{2} ratio exhibited the most stability at F\textsubscript{I}O\textsubscript{2} values ≥ 0.5 and PaO\textsubscript{2} values ≤ 100 mmHg, and the authors concluded that PaO\textsubscript{2}/F\textsubscript{I}O\textsubscript{2} ratio was probably a useful estimation of the degree of gas exchange abnormality under usual clinical conditions. Whiteley et al. also described identical relation with other mathematical models [6, 7].
This nonlinear relation between PaO₂/FiO₂ and FiO₂, however, underlines the limitations describing the intensity of hypoxemia using PaO₂/FiO₂, and is thus of major importance for the clinician. The objective of this note is to describe the relation between PaO₂/FiO₂ and FiO₂ with a simple model, using the classic Berggren shunt equation and related calculation, and briefly illustrate the clinical consequences.

**Berggren shunt equation (Equation 1)**

The Berggren equation [8] is used to calculate the magnitude of intrapulmonary shunt (S), “comparing” the theoretical O₂ content of an “ideal” capillary with the actual arterial O₂ content and taking into account what comes into the lung capillary, i.e., the mixed venous content. Cc’O₂ is the capillary O₂ content in the ideal capillary, CaO₂ is the arterial O₂ content, and CVO₂ is the mixed venous O₂ content.

\[
S = \frac{\dot{Q}_s}{\dot{Q}_I} = \frac{(Cc'O_2 - CaO_2)}{(Cc'O_2 - CVO_2)}
\]

This equation can be written incorporating the arteriovenous difference (AVD) as:

\[
Cc'O_2 - CaO_2 = \left(\frac{S}{1-S}\right) \times \text{AVD}.
\]

Blood O₂ contents are calculated from PO₂ and hemoglobin concentrations as:

**Equation of oxygen content (Equation 2)**

\[
CO_2 = (Hb \times S_2 \times 1.34) + (PO_2 \times 0.0031)
\]

The formula takes into account the two forms of oxygen carried in the blood, both that dissolved in the plasma and that bound to hemoglobin. Dissolved O₂ follows Henry’s law – the amount of O₂ dissolved is proportional to its partial pressure. For each mmHg of PO₂ there is 0.003 ml O₂/dl dissolved in each 100 ml of blood. O₂ binding to hemoglobin is a function of the hemoglobin-carrying capacity that can vary with hemoglobinopathies and with fetal hemoglobin. In normal adults, however, each gram of hemoglobin can carry 1.34 ml of O₂. Deriving blood O₂ content allows calculation of both Cc’O₂ and CaO₂ and allows Eq. 1 to be rewritten as follows:

\[
\left[(Hb \times Sc'O_2 \times 1.34) + (Pc'O_2 \times 0.0031)\right] - \left[(Hb \times SaO_2 \times 1.34) + (PaO_2 \times 0.0031)\right] = \left(\frac{S}{1-S}\right) \times \text{AVD}
\]

In the ideal capillary (c’), the saturation is 1.0 and the Pc’O₂ is derived from the alveolar gas equation:

\[
Pc'O_2 = PAO_2 = (P_B - 47) \times FiO_2 - \frac{PaCO_2}{R}.
\]

This equation describes the alveolar partial pressure of O₂ (PAO₂) as a function, on the one hand, of barometric pressure (P_b), from which is subtracted the water vapor pressure at full saturation of 47 mmHg, and FiO₂, to get the inspired O₂ fraction reaching the alveoli, and on the other hand of PaCO₂ and the respiratory quotient (R) indicating the alveolar partial pressure of PCO₂. Saturation, Sc’O₂ and SaO₂ are bound with O₂ partial pressure (PO₂) Pc’O₂ and PaO₂, by the oxy-hemoglobin dissociation curve, respectively. The oxy-hemoglobin dissociation curve describes the relationship of the percentage of hemoglobin saturation to the blood PO₂. This relationship is sigmoid in shape and relates to the nonlinear relation between hemoglobin saturation and its conformational changes with PO₂. A simple, accurate equation for human blood O₂ dissociation computations was proposed by Severinghaus et al. [9]:

**Blood O₂ dissociation curve equation (Equation 4)**

\[
SO_2 = \left(\left(\frac{PO_2^3 + 150PO_2}{1} \times 23 400\right) + 1\right)^{-1}
\]

This equation can be introduced in Eq. 1:

\[
\left[(Hb \times \left(\left(\left(P_B - 47\right) \times FiO_2 - \frac{PaCO_2}{R}\right)^{-1} + 1\right) \times 1.34\right) + \left((P_B - 47) \times FiO_2 - \frac{PaCO_2}{R}\right)\times 0.0031\right] - \left[(Hb \times \left(\left(PaO_2^3 + 150PaO_2\right) \times 23 400\right) + 1\right) \times 1.34 + (PaO_2 \times 0.0031)\right] = \left(\frac{S}{1-S}\right) \times \text{AVD}
\]

Equation 1 modified gives a relation between FiO₂ and PaO₂ with six fixed parameters: Hb, PaCO₂, the respiratory quotient R, the barometric pressure (P_B), S and AVD. The resolution of this equation was performed here with Mathcad® software, (Mathsoft Engineering & Education, Cambridge, MA, USA).