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PHYSIOLOGICAL NOTE

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Relation between PaO_2/F_IO_2 ratio and F_IO_2: a mathematical description

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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_2 difference, the intrapulmonary shunt fraction, the oxygen index and the PaO_2/F_IO_2 ratio. Of these different indices the PaO_2/F_IO_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_2/F_IO_2 measurement with PEEP set above 10 cmH_2O, but F_IO_2 was still not fixed [3]. Important for this discussion, the PaO_2/F_IO_2 ratio is influenced not only by ventilator settings and PEEP but also by F_IO_2. First, changes in F_IO_2 influence the intrapulmonary shunt fraction, which equals the true shunt plus ventilation–perfusion mismatching. At F_IO_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_IO_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_IO_2 of 1.0 absorption atelectasis may occur, increasing true shunt [4]. Thus, at high F_IO_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_2 difference, the $PaCO_2$ level and the hemoglobin level, the relation between PaO_2/F_IO_2 ratio and F_IO_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_IO_2 between 0.21 and 1.0. Five indices of O_2 exchange efficiency were calculated (PaO_2/F_IO_2, venous admixture, $P(A\text{-}a)O_2$, PaO_2/alveolar PO_2, and the respiratory index). They described a curvilinear shape of the curve for PaO_2/F_IO_2 ratio as a function of F_IO_2, but PaO_2/F_IO_2 ratio exhibited the most stability at F_IO_2 values ≥ 0.5 and PaO_2 values ≤ 100 mmHg, and the authors concluded that PaO_2/F_IO_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 PaO_2/F_IO_2 and F_IO_2, however, underlines the limitations describing the intensity of hypoxemia using PaO_2/F_IO_2, and is thus of major importance for the clinician. The objective of this note is to describe the relation between PaO_2/F_IO_2 and F_IO_2 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 O_2 content of an "ideal" capillary with the actual arterial O_2 content and taking into account what comes into the lung capillary, i.e., the mixed venous content. $Cc'O_2$ is the capillary O_2 content in the ideal capillary, CaO_2 is the arterial O_2 content, and $C\bar{v}O_2$ is the mixed venous O_2 content,

$$S = \frac{\dot{Q}s}{\dot{Q}t} = \frac{(Cc'O_2 - CaO_2)}{(Cc'O_2 - C\bar{v}O_2)}$$

This equation can be written incorporating the arterio-venous difference (AVD) as:

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

Blood O_2 contents are calculated from PO_2 and hemoglobin concentrations as:

Equation of oxygen content (Equation 2)

$$CO_2 = (\text{Hb} \times SO_2 \times 1.34) + (PO_2 \times 0.0031)$$

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 O_2 follows Henry's law – the amount of O_2 dissolved is proportional to its partial pressure. For each mmHg of PO_2 there is 0.003 ml O_2/dl dissolved in each 100 ml of blood. O_2 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 O_2. Deriving blood O_2 content allows calculation of both $Cc'O_2$ and CaO_2 and allows Eq. 1 to be rewritten as follows:

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

In the ideal capillary (c′), the saturation is 1.0 and the $Pc'O_2$ is derived from the alveolar gas equation:

$$Pc'O_2 = PAO_2 = (P_B - 47) \times F_IO_2 - \frac{PaCO_2}{R}.$$

This equation describes the alveolar partial pressure of O_2 (PAO_2) 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 F_IO_2, to get the inspired O_2 fraction reaching the alveoli, and on the other hand of $PaCO_2$ and the respiratory quotient (R) indicating the alveolar partial pressure of PCO_2. Saturation, $Sc'O_2$ and SaO_2 are bound with O_2 partial pressure (PO_2) $Pc'O_2$ and PaO_2, by the oxy-hemoglobin dissociation curve, respectively. The oxy-hemoglobin dissociation curve describes the relationship of the percentage of hemoglobin saturation to the blood PO_2. This relationship is sigmoid in shape and relates to the nonlinear relation between hemoglobin saturation and its conformational changes with PO_2. A simple, accurate equation for human blood O_2 dissociation computations was proposed by Severinghaus et al. [9]:

Blood O_2 dissociation curve equation (Equation 4)

$$SO_2 = \left(\left(\left(PO_2^3 + 150PO_2\right)^{-1} \times 23\,400\right) + 1\right)^{-1}$$

This equation can be introduced in Eq. 1:

$$\begin{aligned}&\left[\left(\text{Hb} \times \left(\left(\left(\left((P_B - 47) \times F_IO_2 - \frac{PaCO_2}{R}\right)^3\right.\right.\right.\right.\right.\\ &\left.\left. + 150\left((P_B - 47) \times F_IO_2 - \frac{PaCO_2}{R}\right)\right)^{-1}\\ &\left.\left.\left.\times 23\,400\right) + 1\right)^{-1} \times 1.34\right) + \left(\left((P_B - 47)\right.\right.\\ &\left.\left.\left.\times F_IO_2 - \frac{PaCO_2}{R}\right) \times 0.0031\right)\right]\\ &-\left[\left(\text{Hb} \times \left(\left(\left(PaO_2^3 + 150PaO_2\right)^{-1} \times 23\,400\right)\right.\right.\right.\\ &\left.\left.\left. + 1\right)^{-1} \times 1.34\right) + (PaO_2 \times 0.0031)\right)\right]\\ &= \left(\frac{S}{1-S}\right) \times \text{AVD}\end{aligned}$$

Equation 1 modified gives a relation between F_IO_2 and PaO_2 with six fixed parameters: Hb, $PaCO_2$, 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).

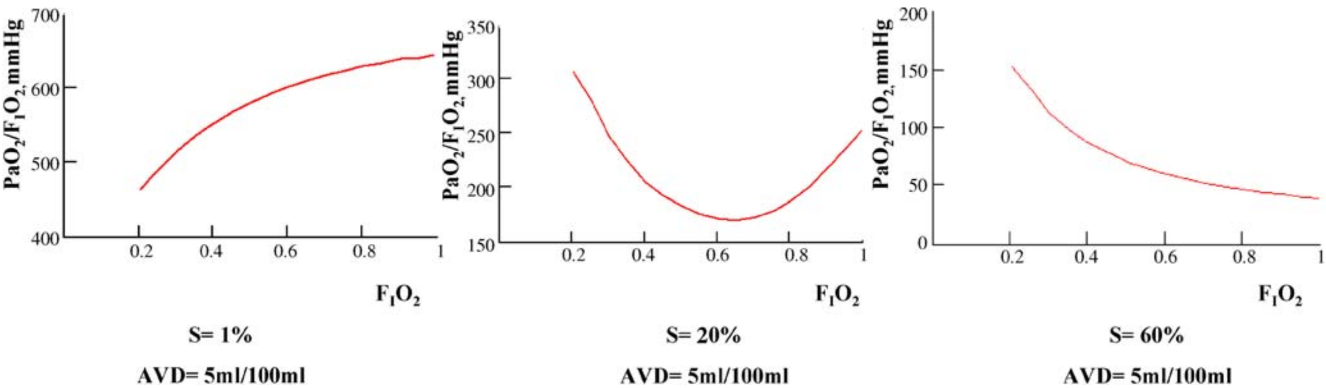

Fig. 1 Relation between PaO_2/FIO_2 and FIO_2 for a constant arterio-venous difference (*AVD*) and different shunt levels (*S*)

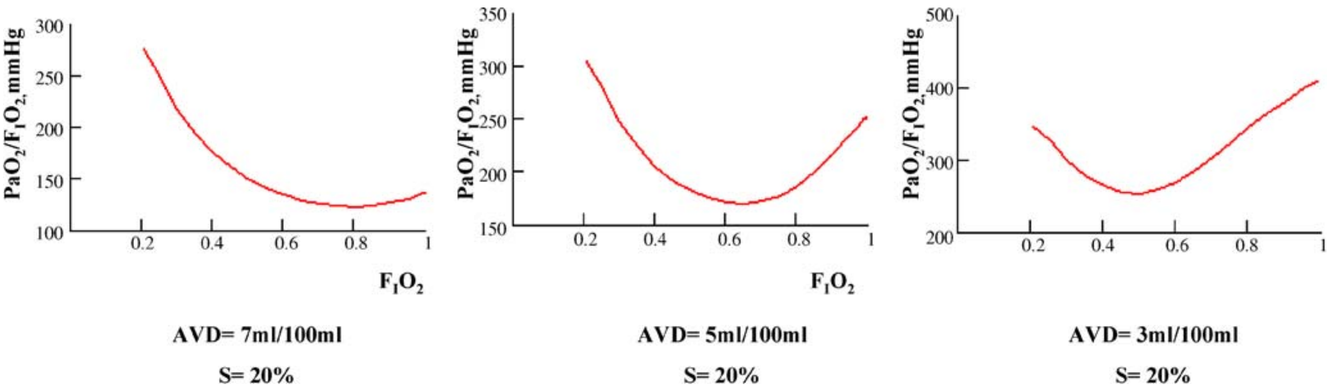

Fig. 2 Relation between PaO_2/FIO_2 and FIO_2 for a constant shunt (*S*) level and different values of arterio-venous differences (*AVD*)

Resolution of the equation

The equation results in a nonlinear relation between F_IO_2 and PaO_2/F_IO_2 ratio. As previously mentioned, numerous factors, notably nonpulmonary factors, influence this curve: intrapulmonary shunt, AVD, $PaCO_2$, respiratory quotient and hemoglobin. The relationship between PaO_2/F_IO_2 and F_IO_2 is illustrated in two situations. Figure 1 shows this relationship for different shunt fractions and a fixed AVD. For instance, in patients with 20% shunt (a frequent value observed in ARDS), the PaO_2/F_IO_2 ratio varies considerably with changes in F_IO_2. At both extremes of F_IO_2, the PaO_2/F_IO_2 is substantially greater than at intermediate F_IO_2. In contrast, at extremely high shunt ($\cong 60\%$) PaO_2/F_IO_2 ratio is greater at low F_IO_2 and decreases at intermediate F_IO_2, but does not exhibit any further increase as inspired F_IO_2 continue to increase, for instance above 0.7. Figure 2 shows the same relation but with various AVDs at a fixed shunt fraction. The larger is AVD, the lower is the PaO_2/F_IO_2 ratio for a given F_IO_2. AVD can vary substantially with cardiac output or with oxygen consumption.

These computations therefore illustrate substantial variation in the PaO_2/F_IO_2 index as F_IO_2 is modified under conditions of constant metabolism and ventilation–perfusion abnormality.

Consequences

This discussion and mathematical development is based on a mono-compartmental lung model and does not take into account dynamic phenomena, particularly when high F_IO_2 results in denitrogenation atelectasis. Despite this limitation, large nonlinear variation and important morphologic differences of PaO_2/F_IO_2 ratio curves vary markedly with intrapulmonary shunt fraction and AVD variation. Thus, not taking into account the variable relation between F_IO_2 and the PaO_2/F_IO_2 ratio could introduce serious errors in the diagnosis or monitoring of patients with hypoxemia on mechanical ventilation.

Recently, the accuracy of the American–European consensus ARDS definition was found to be only moderate when compared with the autopsy findings of diffuse alveolar damage in a series of 382 patients [10]. The problem discussed here with F_IO_2 may to some extent participate in these discrepancies. A study by Ferguson et al. [11] illustrated the clinical relevance of this discussion. They sampled arterial blood gases immediately after initiation of mechanical ventilation and 30 min after resetting the ventilator in 41 patients who had early ARDS based on the most standard definition [2]. The changes in ventilator settings chiefly consisted of increasing F_IO_2 to 1.0. In 17 patients (41%), the hypoxemia criterion for ARDS persisted after this change ($PaO_2/F_IO_2 < 200$ mmHg), while in the other 24 patients (58.5%) the PaO_2/F_IO_2 had become greater than 200 mmHg after changing the F_IO_2, essentially "curing" them of their ARDS in a few minutes. Of note, outcome varied greatly between the "persistent" and "transient" ARDS groups. There was a large difference in mortality, and duration of ventilation, favoring the "transient" ARDS group. Thus, varying F_IO_2 will alter the PaO_2/F_IO_2 ratio in patients with true and relative intrapulmonary shunt of $\geq 20\%$. In clinical practice, when dealing with patients with such shunt levels, one should know that the increasing PO_2/F_IO_2 with F_IO_2 occurs only after F_IO_2 increase to > 0.6 (depending on the AVD value). Thus, the use of the PO_2/F_IO_2 ratio as a dynamic variable should be used with caution if F_IO_2, as well as other ventilatory settings, varies greatly.

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