ILLUMINATIONS | Curricular Integration of Physiology

Teaching an intuitive derivation of the clinical alveolar equations: mass balance as a fundamental physiological principle

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INTRODUCTION

Every student of pulmonary physiology comes across two essential equations of ventilation and gas exchange, the alveolar ventilation equation (“the CO₂ equation”) and the alveolar gas equation (“the O₂ equation”). These equations are particularly relevant for health professions students, given both their physiological significance and tremendous utility in clinical practice.

For equations of such importance, it may be surprising that, in educational resources, they are typically presented outright with minimal justification (2) or derived with abbreviated or simplified methods (3); seldom, even in medical textbooks, are complete and rigorous derivations presented. ¹ Sometimes derivations are omitted when teaching equations because they are either not intuitive or overly complex. However, in the case of the alveolar equations, there is a wealth of physiological reasoning behind their derivations, which involve only algebra, and are accessible across all levels of medical training.

Central to deriving and understanding the equations is the principle of mass balance, the idea that substances accumulate within and leave systems based on the relative rates with which they enter and exit these systems. Steady-state equilibrium occurs when the rates of entry and exit are equal. The concept of mass balance is relevant to the physiology of multiple organ systems.

The intuition and utility of mass balance is perhaps best illustrated with the pulmonary alveolar equations because of the multistep process needed for their derivations. While the seminal paper by Fenn et al. (5) on the alveolar gas equation presents fascinating graphs that have been cited as a learning opportunity (4), their derivation uses antiquated notation, is difficult to follow for the typical medical student, and does not present fascinating graphs that have been cited as a learning opportunity (4), their derivation uses antiquated notation, is difficult to follow for the typical medical student, and does not present complete and rigorous derivations presented. ¹ Sometimes derivations are omitted when teaching equations because they are either not intuitive or overly complex. However, in the case of the alveolar equations, there is a wealth of physiological reasoning behind their derivations, which involve only algebra, and are accessible across all levels of medical training.

Review of Foundational Concepts

We introduce terms (Table 1) and prerequisite physiological concepts by briefly reviewing three essential pulmonary topics: dead space, the respiratory quotient, and ventilation-perfusion mismatch. Consistent with the modern literature, we use Newton’s dot notation with volumes to convey rates of volume change or flow.

Dead space. The ultimate goal of breathing is to maintain homeostasis by replenishing O₂ and eliminating CO₂ in proportion to the demands of ongoing aerobic respiration. The motivation for considering dead space is that gas exchange only occurs in the alveoli, whereas standing in between the environment and the alveoli are the conducting airways, air passages with no gas exchange potential. This means that the rate at which air is moved in and out of the lungs (the minute ventilation, V˙E) is not the rate at which fresh air is moved in and out of the alveoli (the alveolar ventilation, V˙A). This is because a portion of every breath can be thought of as “wasted,” or stuck in the conducting airways without any gas exchange potential, the so-called dead space ventilation (V˙D). Thus, we can write:

\[ V˙E = V˙A + V˙D \]

(1)

During normal breathing, the brain controls the respiratory rate (RR) and the volume of air inhaled/exhaled, termed the tidal volume (VT). Just as cardiac output can be broken down into heart rate times stroke volume, V˙E can be expressed as RR times VT and V˙D as RR times dead space volume (V˙D). Thus, with RR, VT, and V˙D, we can rewrite Eq. 1 as:

\[ V˙A = V˙E - V˙D \]


\[
\dot{V}_A = RR(V_T - V_D)
\]

(2)

These forms of the dead space equation tell us three important things:

- If all else is constant, \( \dot{V}_A \) decreases with increasing \( V_D \).
- If all else is constant, \( \dot{V}_A \) increases with increasing \( RR \) and \( V_T \).
- Holding \( V_E = RR \cdot V_T \) constant, \( \dot{V}_A \) decreases with increasing \( RR \) (and corresponding decreasing \( V_T \)).

Breathing faster or deeper can both enhance gas exchange. However, rapid shallow breathing tends to be less efficient at gas exchange than slow deep breathing. This is important in the Intensive Care Unit (ICU), where assessing a ventilated patient’s status requires review of not only \( V_E \) but also \( V_T \).

In addition to the anatomic dead space of the conducting airways, physiological \( V_D \) includes the volume of alveolar air that does not participate in normal alveolar respiratory gas exchange. For example, destruction of alveolar walls can result in the coalescing of multiple alveoli, giving rise to enlarged air spaces that are relatively poorly perfused (e.g., emphysema). Conditions such as pulmonary embolism may entirely block perfusion to alveolar capillary units. Increased alveolar dead space explains how these diseases lead to decreased gas exchange with an unchanged \( V_E \). Anatomic and alveolar dead space together are referred to as physiological dead space, which is the true value of \( V_D \) as represented in the equations.

The respiratory quotient. The respiratory quotient (RQ) is the ratio of \( CO_2 \) generated to \( O_2 \) consumed in metabolism:

\[
RQ = \frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}}
\]

Where \( \dot{V}_{CO_2} \) is the rate of \( CO_2 \) generation, and \( \dot{V}_{O_2} \) is the rate of \( O_2 \) consumption. The value of RQ is substrate dependent and changes with the diet. RQ is exactly 1 for all carbohydrates, \( \sim 0.8 \) for proteins, and \( \sim 0.7 \) for fats. We demonstrate this concept by considering the balanced chemical equation for the complete oxidation of glucose:

\[
C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O
\]

The coefficients in this equation show that, for glucose, an equal amount of \( CO_2 \) is generated as \( O_2 \) is consumed (RQ = 1). By changing the starting material, one can derive the RQ for any substrate; for example, RQ = 0.7 for myristic acid. This explains why we adjust RQ for a hospitalized patient on intravenous sugar solution (RQ = 1) or a patient with starvation ketosis (RQ = 0.7). RQ = 0.8 is a clinically accepted value for a Western diet.

Ventilation-perfusion mismatch. Thus far, the discussion has treated the lungs as a single unit of gas exchange that ventilates at \( \dot{V}_A \). In fact, gas exchange occurs within heterogeneous alveolar-capillary units that differ not only in their \( \dot{V}_A \), but also their capillary perfusion \( Q \). The concept has major clinical significance because \( CO_2 \) and \( O_2 \) are transported differently in the blood. A significant fraction of blood \( CO_2 \) is transported as bicarbonate, with smaller fractions transported as carbaminohemoglobin and dissolved \( CO_2 \). The dissociation curve for \( CO_2 \) transported in this fashion is roughly linear in the physiological range. Consequently, high \( \dot{V}_A/Q \) units compensate for low \( \dot{V}_A/Q \) units in overall \( CO_2 \) elimination. In marked contrast, blood \( O_2 \) is mostly transported as oxyhemoglobin, with a miniscule dissolved component. The oxyhemoglobin dissociation curve is markedly nonlinear in the physiological range, being quite flat at \( P_{O_2} > 60 \) mmHg and quite steep at \( P_{O_2} < 60 \) mmHg. Thus high \( \dot{V}_A/Q \) units with a \( P_{O_2} > 60 \) mmHg are on the flat portion of the curve, and there is little increase in \( O_2 \) content as \( P_{O_2} \) is increased further above 60 mmHg. In contrast, \( \dot{V}_A/Q \) units with a \( P_{O_2} < 60 \) mmHg are on the steep portion of the oxyhemoglobin dissociation curve, and small further decreases in \( P_{O_2} \) correspond to comparatively large decreases in \( O_2 \) content. Because of this asymmetry in the effects of changes in \( P_{O_2} \) on \( O_2 \) content between high and low \( \dot{V}_A/Q \) units, increasing \( P_{O_2} \) in high \( \dot{V}_A/Q \) units cannot compensate
for low $V_{A}/Q$ units in overall blood oxygenation; the high $V_{A}/Q$ units contribute far less additional $O_{2}$ content relative to the decreased $O_{2}$ content contributed by the low $V_{A}/Q$ units. Thus any exacerbation of baseline $V_{A}/Q$ heterogeneity in the lungs, termed $V_{A}/Q$ mismatch, decreases overall blood oxygenation, even at a constant overall $V_{A}$ and $Q$. It is important to emphasize that mismatch occurs not only in pathological states, but also in normal, healthy lungs; understanding this fact is key to understanding the clinical utility of the alveolar equations.

The Ventilation Identities

In this section, we split $V_{A}$ into its component gases by using the principle of mass balance to derive fundamental statements about the relationship between the gases in the atmosphere, the gases in the body, and $V_{A}$. Together, the following three equations regarding $N_{2}$, $O_{2}$, and $CO_{2}$ (Eqs. 4, 5, and 6, below) underpin the clinical equations to follow. To highlight their importance, we call them the “ventilation identities.”

We derive the “ventilation identities” with several assumptions:

1. Gas transfer in the lung is at steady state. Steady-state equilibrium is safely assumed in most clinical scenarios. However, with acute changes, such as during the transition between different activity levels or during interval training incorporating bursts of high-intensity exercise, steady state may not be achieved. Sometimes this even leads to the respiratory exchange ratio, the empiric measurement of CO$_{2}$ production versus $O_{2}$ consumption from inspired and expired gases, differing from RQ at the cellular level due to, e.g., lactate production or removal and subsequent bicarbonate buffering. The mathematics of non-steady-state solutions are complex and not adequately represented by the equations we present.

2. Argon and other gases present in trace amounts in the atmosphere are considered as part of nitrogen. This simplifying assumption groups the metabolically inactive gases together (defined in Nitrogen below).

3. There is no CO$_{2}$ or water vapor in the atmosphere. For simplicity, we assume CO$_{2}$ is only expired, not inspired, and the only gases contributing to atmospheric pressure are $N_{2}$ and $O_{2}$.

4. All gases are dry when measured. The airways humidify air, and the presence of water vapor would complicate the application of mass balance to the gases of interest. However, imagine that, for all measured quantities, the water vapor is removed, and the gas is then expanded to occupy its initial volume (which laboratories actually perform!). Because the saturated partial pressure of water vapor is constant at a given temperature, we can make this assumption and then account for water vapor in a simple way in the derivation of the alveolar gas equation.

The reasoning behind the “ventilation identities” can then be expressed as follows: Consider an arbitrary gas $X$ that may be present in the environment or in the body. As a person inspires at inspired alveolar ventilation ($V_{A}I$), some molar fraction of the inspired breath consists of $X$; call it $F_{XI}$. Similarly, as a person expires at expired alveolar ventilation ($V_{AE}$), some molar fraction of expired breath consists of $X$; call it $F_{XE}$ (capital A for “alveolar” to emphasize that the source for non-dead space expiration is alveolar air).

Then, we can express inspired and expired ventilation of gas $X$, respectively, as $F_{XI} \cdot V_{AI}$ and $F_{XE} \cdot V_{AE}$. It is important to separate these terms because $V_{AI}$ is not necessarily equal to $V_{AE}$. Ignoring water vapor (assumption 2), $V_{AE}$ is usually slightly less than $V_{AI}$, since for $RQ = 0.8$, on average there are only about 8 molecules of CO$_{2}$ expired for every 10 molecules of $O_{2}$ inspired. The difference is frequently ignored in casual discussions of breathing, but is crucially important for the derivations that follow.

On balance, the body may consume $X$, generate $X$, or not interact with $X$ at all, and each of the three major gases involved in human respiration interacts with the body in one of these three ways. One confusing point for learners is that, depending on the gas $X$, the quantity $V_{X}$ will not necessarily denote a ventilation, i.e., not necessarily a volume inhaled or exhaled like $V_{A}$; it may represent a rate of generation or consumption, depending on the gas.

Nitrogen. $N_{2}$ is the most abundant gas in the atmosphere, but, for the respiratory system, it is considered a metabolically inactive gas. It is neither produced nor consumed by the body, but rather freely diffuses down its partial pressure difference to equilibrium, such that, at steady state, the same amount of $N_{2}$ is inspired as expired.

Considering inspired and expired $N_{2}$ content as equal, we can express the volume of $N_{2}$ inspired or expired in 1 min as (see Fig. 1A):

\[ V_{NI} = F_{N_{2}} \cdot V_{AI} = F_{N_{2}} \cdot V_{AE} \] (4)

where, as above, $F$ is mole fraction, $A$ is alveolar, $I$ is inspired, and $E$ is expired. $V_{N_{2}}$ is defined, consistent with terms like $V_{A}$ and $V_{E}$, as a ventilation.

In the derivation of the alveolar gas equation, the ventilation identity for $N_{2}$ balances the $V_{AI}$ and $V_{AE}$ values. Teaching this equation also allows students to think explicitly about the physiology of $N_{2}$ in respiration, presenting an opening to discuss important clinical considerations for $N_{2}$:

- Nitrogen’s inertness is thought to be a desirable property in reducing atelectasis; the presence of $N_{2}$ helps maintain a sufficient gas tension within the alveoli to resist collapse (6).
- Nitrogen’s inertness also explains the use of $O_{2}$ therapy in the management of pneumothorax: washing out the nitrogenous component of the ectopic gas facilitates absorption back into the bloodstream and a decrease in the pneumothorax volume (8).

Oxygen. $O_{2}$ is inspired from the environment and flows to the alveoli (Fig. 1B), where some of it diffuses into the bloodstream, mostly binds to hemoglobin, and diffuses into metabolically active tissues to become the final electron acceptor of the electron transport chain. Some $O_{2}$ remains in the alveoli and forms part of the expired breath. Thus, like $N_{2}$, $O_{2}$ is present in both inspired and expired gas, but, unlike $N_{2}$, $O_{2}$ is consumed by the body, so less is expired than inspired.

We can express the volume of $O_{2}$ consumed per minute as:

\[ V_{O_{2}} = V_{AO_{2}} = V_{AI} - F_{AO_{2}} \cdot V_{AE} \] (5)

where it is important to note that $V_{O_{2}}$ is not a ventilation: it denotes rate of $O_{2}$ consumption, not inspiration or expiration.
**Carbon dioxide.** CO₂ is present in negligible amounts in the atmosphere, and we can safely assume it is not a significant part of inspired gas (assumption 3). Assuming a constant $V_A$, it reaches a steady-state pressure in the alveoli, such that it is eliminated at the same rate that it is generated, and thus we can express both the volume of CO₂ eliminated per minute and the volume of CO₂ generated per minute as (see Fig. 1C):

$$\dot{V}_{CO_2} = F_{ACO_2} \cdot \dot{V}_A$$

Note that there is no inspired term because we consider the atmosphere to have negligible CO₂ content. Also note that the definition of $V_{CO_2}$ is again different, this time denoting rate of CO₂ generation or expiration, not inspiration or consumption.

**Accounting identities.** The “ventilation identities” addressed mass balance for individual gases. Their independent contributions to $V_A$ and $V_E$ compose total ventilation (Dalton’s law). We can easily derive:

$$\dot{V}_A = \text{inspired } O_2 + \text{inspired } N_2$$

$$\dot{V}_A = F_{IO_2} \cdot \dot{V}_A + F_{IN_2} \cdot \dot{V}_A$$

$$\dot{V}_E = \text{expired } O_2 + \text{expired } N_2 + \text{expired } CO_2$$

$$\dot{V}_E = F_{AO_2} \cdot \dot{V}_E + F_{AN_2} \cdot \dot{V}_E + F_{ACO_2} \cdot \dot{V}_E$$

obtaining the simple intuition that the mole fractions of constituent gases sum to 1.

**The Clinical Alveolar Equations.**

We now have all of the ingredients necessary to derive the alveolar equations used in clinical practice and conceptually understand them; Table 2 summarizes the building blocks of these equations. The basic road map is as follows: the alveolar ventilation equation is a simple transformation of the ventilation identity for CO₂. Substituting the dead space Eq. 2 for $V_A$ yields the clinically useful form.

The alveolar gas equation results from the combination of all of the “ventilation identities.” A simplifying assumption yields the clinically used form and understanding the nature of this assumption is crucial for grasping its limitations.

**The alveolar ventilation equation.** Derivation. Consider Eq. 6, the ventilation identity for CO₂. By Dalton’s law of partial pressures, the partial pressure of a gas ($P_X$) is directly proportional to its mole fraction ($F_X$).

We then have:

$$\dot{V}_{CO_2} = kP_{ACO_2} \cdot \dot{V}_E$$

where $P$ denotes partial pressure, and $k$ is a proportionality constant. Rearranging terms, we have:

$$P_{ACO_2} = \frac{k\dot{V}_{CO_2}}{\dot{V}_A}$$

where it is understood that $V_A$ refers to $V_{AE}$, and we redefine $k$ as its reciprocal to follow convention. This is the basic alveolar ventilation equation.

**Table 2. Building blocks of the alveolar equations**

| Equation | Description |
|----------|-------------|
| $V_{N_2} = F_{IN_2} \cdot \dot{V}_A + F_{AN_2} \cdot \dot{V}_E$ | Ventilation identity for N₂ |
| $V_{CO_2} = F_{ACO_2} \cdot \dot{V}_E$ | Ventilation identity for CO₂ |
| $V_{O_2} = F_{IO_2} \cdot \dot{V}_A - F_{AO_2} \cdot \dot{V}_E$ | Ventilation identity for O₂ |
| $1 = F_{IO_2} + F_{IN_2}$ | Accounting identity for inspiration |
| $1 = F_{AO_2} + F_{AN_2} + F_{ACO_2}$ | Accounting identity for expiration |
| $RQ = \frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}}$ | Respiratory quotient definition |
| $V_A = RR \cdot VT \left(1 - \frac{\dot{V}_I}{\dot{V}_T}\right)$ | Dead space clinical equation |

See Table 1 for definition of terms used.
At body temperature ($T_B$) of 37°C (310K), $k = 863$ mmHg. This constant comes from the fact that, by historical convention, the three quantities in Eq. 9 are expressed under different conditions of temperature, pressure, and humidity. The constant $k$ accounts for physical conditions as well as for proportionality. It is possible to derive $k = RT = (760/273) T_B$, where $R$ is the ideal gas constant expressed in L BTPS-mmHg·L STPD$^{-1}$·K$^{-1}$, 760 mmHg is standard pressure, and 273K is standard temperature (5, 9). Thus, while $k$ is $T_B$-dependent, the physiological range of $T_B$, e.g., during a fever, is relatively small, making $k = 863$ mmHg an appropriate value for most physiological applications of the alveolar ventilation equation.

Two adjustments to Eq. 9 greatly increase its clinical utility. First, due to the approximately linear CO2 dissociation curve and the resultant compensation of high VA/Q units for low VA/Q units with respect to CO2 elimination, the arterial CO2 pressure ($P_{ACO2}$) is a reasonable surrogate for alveolar CO2 pressure ($P_{ACO2}$). Second, while $V_A$ is not a readily accessible value in clinical practice, Eq. 2 expresses $V_A$ in terms of clinical parameters. Substituting $P_{ACO2}$ for $P_{ACO2}$ and Eq. 2 for $V_A$, we have:

$$PaCO_2 = \frac{kVCO_2}{RR \cdot VT \left(1 - \frac{VD}{VT}\right)} \quad (10)$$

We call Eq. 10 the clinical alveolar ventilation equation because of its utility in clinical practice. $PaCO_2$ can be measured on a routine blood gas or approximated through waveform capnography. Additionally, patients on ventilators have both known RR and VT values. Thus most of the values in the equation are known, especially for mechanically ventilated patients. As such, while Eq. 9 clearly illustrates the fundamental relationship between the generation of CO2, the elimination of CO2 through breathing, and the CO2 that remains in the body, Eq. 10 provides a more clinically oriented variant that we believe can help clinicians reason through the differential diagnosis of perturbations in $P_{ACO2}$.

**CLINICAL APPLICATIONS: THE DETERMINATION OF CARBON DIOXIDE STATUS.** We present three short clinical applications to illustrate the utility of the clinical $V_A$ equation to students:

1. $VCO_2$ can be measured with exhaled gas analysis, but is more commonly estimated in clinical practice. Perhaps even more powerful than knowing this parameter at discrete points in time is the fact that it depends directly on the rate of metabolism. This means that the more metabolically active a person is, the greater the rate at which he/she will generate CO2 (and require O2). That is why intensive care unit clinicians may deeply sedate or even paralyze severely hypoxemic patients; by lowering their metabolic rate, they are helping to keep their CO2 levels down (and O2 levels up) and reduce their ventilatory demand (Fig. 2A).

2. A clinical case example: An intern leaves a mechanically ventilated patient stable, sedated, and paralyzed at the end of a shift. The next morning, an arterial blood gas is performed, and the $PaCO_2$ has risen substantially, despite no change in ventilator settings. What happened overnight? From Eq. 10, the right-hand side of the equation must have increased.

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**Fig. 2.** Key relationships in the clinical alveolar ventilation ($V_A$) equation. These stylized relationships assume all variables not in the figures are constant and do not provide physiological compensation. Default values are as follows: $k = 863$ mmHg; $VCO_2 = 0.2$ L/min; RR = 12/min; VT = 0.5 Liters; VT = 0.15 Liters. A: at constant $V_A$, the higher the rate of CO2 generation ($VCO_2$), the higher the $PaCO_2$. B: $PaCO_2$ increases as dead space ($VD$) increases, decreasing $V_A$ when $VE$ is constant. Dead space diseases such as pulmonary embolism can cause hypercapnia through this mechanism. C: the same $VE$ can result in markedly different $PaCO_2$, depending on the respiratory rate (RR) and VT. As RR increases at a constant $VE$, VT necessarily decreases, resulting in increased dead space ventilation ($VD$) and increased $PaCO_2$. Thus, in general, slow, deep breathing is more efficient for gas exchange than rapid, shallow breathing. See Table 1 for definitions of terms used.
Assuming the patient was sedated, still, afebrile, and had no change in nutrition, then \( \dot{V}_{CO_2} \) should not have changed. Additionally, the ventilator maintained a constant RR and \( V_T \). Therefore, the physiological dead space must have increased. A sudden rise in physiological dead space in a critically ill patient should raise concern for venous thromboembolism (Fig. 2B).

3. An oft-cautioned fatal mistake in clinical medicine is the case of a patient who presents to the emergency room in distress and breathing rapidly. The trainee who sees him/her prescribes a benzodiazepine to help calm his/her “hyperventilation.” The patient subsequently becomes severely academic. It turns out that the rapid breathing was not hyperventilation, but rather a physiological response to an elevated \( C_0_2 \). When respiratory drive was depressed by the drug, \( C_0_2 \) levels increased even further. For example:

\[
\text{RR} = 30 \text{ breaths/min (tachypnea)}
\]

\[
\dot{V}_T = 0.3 \text{ Liters (shallow breathing)}
\]

\[
\dot{V}_D = 0.2 \text{ Liters (increased dead space)}
\]

\[
\dot{V}_{CO_2} = 0.25 \text{ L/min (elevated metabolism; in distress)}
\]

\[
P_{aCO_2} = \frac{k \dot{V}_{CO_2}}{RR \cdot \dot{V}_T \left(1 - \frac{V_D}{\dot{V}_T}\right)}
\]

\[
= \frac{863 \cdot 0.25}{30 \cdot 0.3 \left(1 - \frac{0.2}{0.3}\right)}
\]

\[
= 72 \text{ mmHg (normative : 40 mmHg)}
\]

This case illustrates the fact that multiple variables impact \( C_0_2 \) status, and, specifically, a tachypneic patient is not necessarily hypocapnic (Fig. 2C). A disciplined analysis of Eq. 10 shows that RR is only part of the expression that determines \( P_{aCO_2} \), which means one cannot assume a carbon dioxide level by simply observing a patient’s RR. The only way to know \( P_{aCO_2} \) is to draw a blood gas (or approximate a level through waveform capnography), highlighting the value of blood-gas analysis in clinical care.

The alveolar gas equation. RATIONALE AND METHOD. Unlike the case for \( C_0_2 \), a simple blood test is not a good proxy for the alveolar partial pressure of \( O_2 \) (\( P_{aO_2} \)); arterial partial pressure of \( O_2 \) (\( P_{aCO_2} \)) is normally less than \( P_{aO_2} \). This is largely due to the relatively flat oxyhemoglobin dissociation curve at \( P_0_2 \) values greater than 60 mmHg. Recall from Ventilation-perfusion mismatch above that, for overall blood oxygenation, high \( V_A/Q \) units cannot compensate for low \( V_A/Q \) units. Therefore, when oxygenated blood from all the alveolar-capillary units mixes in the systemic arterial system, \( O_2 \) content is less than that which corresponds to overall \( P_{aO_2} \) (\( P_{aCO_2} < P_{aO_2} \)). There is also a small contribution from natural shunts of venous blood from the bronchial and thebesian veins to arterial blood. These vascular shunts occur downstream from the pulmonary capillaries, decreasing arterial \( O_2 \) saturation from what would be expected based on pulmonary gas exchange.

The difference between \( P_{aO_2} \) and \( P_{aCO_2} \) is referred to as the (A-a)\( P_0_2 \) difference:

\[
(A-a)P_0_2 \text{ difference} = P_{aO_2} - P_{aCO_2} \quad (11)
\]

\( P_{aO_2} \) is determined with an arterial blood-gas measurement. Getting at \( P_{aO_2} \) is the goal of the alveolar gas equation. We will exploit the fact that the RQ ties \( O_2 \) and \( C_0_2 \) levels together and is a clinically obtainable value.

DERIVATION. Almost all of the equations in Table 2, the “ventilation identities” (Eqs. 4–6), the accounting identities (Eqs. 7 and 8), and the RQ formula (Eq. 3), compose this derivation. Specifically, substituting all of these equations into each other yields the alveolar gas equation.

Ultimately, we want to isolate \( F_{aO_2} \), which is directly proportional to our quantity of interest, \( P_{aO_2} \). The easiest place to start is by substituting Eqs. 5 and 6 into Eq. 3:

\[
RQ = \frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}}
\]

\[
= \frac{F_{aCO_2} \cdot \dot{V}_{AE}}{F_{IO_2} \cdot \dot{V}_{AI} - F_{aO_2} \cdot \dot{V}_{AE}} \quad (12)
\]

We know RQ (we are prepared to approximate it as 0.8), we know \( F_{IO_2} \) (0.21 in ambient air, or set by an assisted breathing device), and we know \( F_{aCO_2} \) (determined by \( P_{aCO_2} \)). What to do about \( \dot{V}_{AI} \) and \( \dot{V}_{AE} \)? They are related by the fractional \( N_2 \) concentration because, by Eq. 4, \( N_2 \) content is equal in inspired and expired air (Fig. 1A), and by Eqs. 7 and 8, \( N_2 \) is related to \( O_2 \) and \( CO_2 \) by their mole fractions summing to 1! By Eq. 4:

\[
\dot{V}_{AI} = \frac{\dot{V}_{N_2}}{F_{IO_2}}
\]

\[
\dot{V}_{AE} = \frac{\dot{V}_{N_2}}{F_{aCO_2}} \quad (13)
\]

And substituting in Eqs. 7 and 8:

\[
\dot{V}_{AI} = \frac{\dot{V}_{N_2}}{1 - F_{IO_2}}
\]

\[
\dot{V}_{AE} = \frac{\dot{V}_{N_2}}{1 - F_{aO_2} - F_{aCO_2}} \quad (14)
\]

Substituting Eqs. 13 and 14 into Eq. 12, we get:

\[
RQ = \frac{\dot{V}_{N_2}}{1 - F_{aO_2} - F_{aCO_2}}
\]

\[
= \frac{F_{IO_2} \cdot \dot{V}_{N_2} - F_{aO_2} \cdot \dot{V}_{N_2}}{1 - F_{IO_2}}
\]

\[
= \frac{F_{IO_2} \cdot \dot{V}_{N_2}}{1 - F_{aO_2} - F_{aCO_2}}
\]

From here, careful algebraic manipulation isolates \( F_{aO_2} \), giving:
We call Eq. 17 the clinical alveolar gas equation because of its utility in quickly generating an estimate for $P_{A\text{O}_2}$ at the bedside. We use this along with $P_{A\text{O}_2}$ to compute the $(A-a)P_{O_2}$ difference. In brief, the utility of this number is that we can separate problems with oxygenation into problems with $O_2$ supply to the alveoli (associated with a normal $(A-a)P_{O_2}$ difference) and problems with gas exchange between the alveoli and pulmonary capillaries (associated with an elevated $(A-a)P_{O_2}$ difference). The former includes low $P_{B}$, low $F_{I\text{O}_2}$, (Fig. 3A), and hypoventilation (Fig. 3B). None of these affect gas exchange, so $P_{A\text{O}_2}$ and $P_{A\text{O}_2}$ drop about equally, and the $(A-a)P_{O_2}$ difference is unchanged. The latter includes shunt, $V_{A}/Q$ mismatch, and diffusion limitation. With respect to $O_2$, unaffected lung has little ability to compensate for affected lung, so $P_{A\text{O}_2}$ drops without major effects on $P_{A\text{O}_2}$, widening the $(A-a)P_{O_2}$ difference. Thus the $(A-a)P_{O_2}$ difference is a useful tool in narrowing the differential diagnosis of hypoxemia.

Equation 17 should be used with caution for patients on supplemental $O_2$. For two reasons. First, as $F_{I\text{O}_2}$ increases, the assumption that simplifies Eq. 16 to Eq. 17 becomes increasingly inaccurate (although this inaccuracy is negligible when low levels of supplemental oxygen are used). Using Eq. 16 overcomes this limitation. Second, the $(A-a)P_{O_2}$ difference in healthy lungs increases as $F_{I\text{O}_2}$ increases due to amplified effects of physiological $V_{A}/Q$ mismatch and physiological vascular shunts. $(A-a)P_{O_2}$ difference increases from roughly 10 mmHg at $F_{I\text{O}_2}$ to 40 mmHg or higher at $F_{I\text{O}_2} = 0.9$ (7). Thus the evaluation of whether a patient on supplemental oxygen has an abnormal $(A-a)P_{O_2}$ difference requires adjustment for $F_{I\text{O}_2}$, and there is no universally accepted clinical standard for making this adjustment. Rather than revert to Eq. 16 and reference an $F_{I\text{O}_2}$-dependent $(A-a)P_{O_2}$ difference, clinicians more commonly use the $P/F$ ratio, defined by $P/F$ ratio $= P_{A\text{O}_2}/F_{I\text{O}_2}$. This indicator has utility in diagnosing gas exchange pathology in patients on supplemental $O_2$, but, as merely an estimate itself, also has important limitations (10).

It may be tempting to examine the inverse relationship between $P_{A\text{CO}_2}$ and $P_{A\text{O}_2}$ in the alveolar gas equation and con-
clude it is causal. However, the concept of RQ implies that CO₂ production and O₂ consumption are tied together in metabolism by the contents of the diet and cannot vary independently. A common misconception identifies disease processes that cause both hypercapnia and hypoxemia, such as chronic obstructive pulmonary disease and global hypoventilation, as primary problems with excess carbon dioxide. This reasoning contains an error of confounding; it fails to take into account that alveolar carbon dioxide cannot exogenously increase (unless it is given by medical intervention), but rather is endogenously determined by factors in Eq. 10, such as Vₐ and dead space, which simultaneously affect alveolar oxygen (Fig. 3B).

**CLINICAL APPLICATION: TWO PATIENTS WITH HEROIN OVERDOSE.**

We use the following simple application with example numbers to show students how calculation of the (A-a)PO₂ difference can inform the care of an acutely ill patient.

Assume two patients present simultaneously to an Emergency Department with a heroin overdose. They are breathing ambient air but appear somnolent with slow, shallow breathing.

You perform an arterial blood gas on each patient:

- **Patient A:** PaCO₂ = 60 mmHg; pH = 7.24; PaO₂ = 65 mmHg
- **Patient B:** PaCO₂ = 60 mmHg; pH = 7.24; PaO₂ = 45 mmHg

From the elevated PaCO₂, you conclude both patients are hypoventilating; however, you wish to know if further evaluation is necessary. You now calculate the alveolar O₂ tension (note that it is the same for both patients) assuming RQ = 0.8 and a Ps near sea level:

\[
\text{PAO}_2 = \frac{F_{iO}_2 (P_B - 47) - 60}{0.8}
\]

\[
= (0.21)(760 - 47) - 75
\]

\[
= 75 \text{ mmHg}
\]

Finally, you calculate the (A-a)PO₂ difference for each patient:

- **Patient A:** (A-a)PO₂ difference = 75 - 65 = 10 mmHg
- **Patient B:** (A-a)PO₂ difference = 75 - 45 = 30 mmHg

**Patient A** has a nonelevated (A-a)PO₂ difference and most likely is simply hypoventilating due to the effects of heroin. **Patient B,** on the other hand, has an elevated (A-a)PO₂ difference, which should raise concern for pulmonary parenchymal pathology in addition to hypoventilation. Could he/she have aspirated? Does he/she have an underlying respiratory condition? For **patient B,** these possibilities need to be explored.

**DISCUSSION**

In this paper, we present a framework for thinking about gas exchange based on the principle of mass balance, with the “ventilation identities,” and then use it to derive two key equations for CO₂ and O₂: the alveolar ventilation equation and the alveolar gas equation. This process, involving only algebra, allows educators to organically teach many important concepts in respiratory physiology and link these concepts to the care of acutely ill patients.

Although asking students to independently derive these equations will never be a required part of a health professions curriculum (and, indeed, is not the goal of this approach), many find their understanding of pulmonary physiology enhanced by exposure to the derivations. For the pulmonary module of our organ system-based curriculum, we offered a document covering the derivations and a review session covering the document as optional resources to students. Students who attended rated this session 4.08/5 and found it a helpful adjunct to the content provided in lectures. Narrative feedback focused on the utility of linking foundational physiology with clinical practice and the satisfaction of knowing the origin of these key equations.

We encourage educators to consider incorporating the framework in this document when teaching pulmonary physiology. We hope the clinical applications that were mentioned, in particular, help curriculum leaders in the health professions think about integration of physiology with clinical medicine across the basic medical sciences.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

M.C.W. conceived and designed research; M.C.W. and D.R.M. prepared figures; M.C.W. drafted manuscript; M.C.W., T.C.C., D.R.M., and J.M.W. edited and revised manuscript; M.C.W., T.C.C., D.R.M., and J.M.W. approved final version of manuscript.

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