The physiological basis of pulmonary gas exchange: implications for clinical interpretation of arterial blood gases

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ABSTRACT The field of pulmonary gas exchange is mature, with the basic principles developed more than 60 years ago. Arterial blood gas measurements (tensions and concentrations of O_2 and CO_2) constitute a mainstay of clinical care to assess the degree of pulmonary gas exchange abnormality. However, the factors that dictate arterial blood gas values are often multifactorial and complex, with six different causes of hypoxaemia (inspiratory hypoxia, hypoventilation, ventilation/perfusion inequality, diffusion limitation, shunting and reduced mixed venous oxygenation) contributing variably to the arterial O_2 and CO_2 tension in any given patient. Blood gas values are then usually further affected by the body's abilities to compensate for gas exchange disturbances by three tactics (greater O_2 extraction, increasing ventilation and increasing cardiac output). This article explains the basic principles of gas exchange in health, mechanisms of altered gas exchange in disease, how the body compensates for abnormal gas exchange, and based on these principles, the tools available to interpret blood gas data and, quantitatively, to best understand the physiological state of each patient. This understanding is important because therapeutic intervention to improve abnormal gas exchange in any given patient needs to be based on the particular physiological mechanisms affecting gas exchange in that patient.

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Introduction

The reason we have a lung is well known: to allow the exchange of gases between the air we breathe and the pulmonary capillary blood. We are primarily concerned with two gases, O_2 and CO_2, but what follows applies in concept to all gases (that are not chemically reactive with tissues). Moreover, it does not matter whether the gas is being passed from air to blood (*e.g.* O_2) or from blood to gas (*e.g.* CO_2) because the principles governing gas exchange apply equally in both directions. By exchanging gases, the lungs form one critical part of the O_2/CO_2 transport pathway (fig. 1), the rest of which involves the entire cardiovascular system (heart, vasculature and blood) as well as the body tissues. The entire system, not just the lungs, needs to be considered when interpreting arterial blood gases because each component may affect the others (see section on causes of hypoxaemia below).

The lungs are a collection of some 300 million very small gas-filled polyhedrons (alveoli), the walls of which are made up of little more than a rich capillary network supported by a very thin interstitial matrix. Each alveolus expands with fresh gas (high in O_2 and low in CO_2) that has flowed down the bronchial tree from the mouth during inspiration. The alveoli then reduce in volume during expiration, returning gas (lower in O_2 and higher in CO_2) up the bronchial tree to the mouth. This process is of course called ventilation. The capillaries in the alveolar wall are fed pulmonary arterial blood returned from the tissues. This blood is low in O_2 and high in CO_2, but after the blood has flowed through the alveolus and reaches the pulmonary veins, O_2 has been raised and CO_2 lowered through the gas exchange process. Normally, all alveoli are both ventilated and perfused. While these statements may be self-evident to most, they become the central concept behind how gas exchange occurs and therefore how blood gas numbers can be used clinically.

The structure of the lung has evolved to meet the gas exchange needs on the basis of an overarching, major principle: The exchange of gases between the alveolar gas and the blood occurs by simple, passive diffusion (fig. 1). There is no active transport involved in alveolar gas exchange, and the process of diffusion requires no energy expenditure by the organism. Of course, both ventilation and perfusion are convective processes that do require energy expenditure, and in many common cardiorespiratory diseases, either or both may be compromised.

This article will first explain quantitative aspects of gas exchange based on the above basic principles, starting with the simplest proposition: that of a uniform lung in which all 300 million alveoli are equally perfused and equally ventilated. Real lungs, even in health, are however far from uniform in this regard [1, 2], and this heterogeneity has negative consequences for gas exchange that will next be discussed. The multiple possible causes of abnormal gas exchange will then be summarised, and this will lead to a scheme for interpreting gas exchange findings in clinical settings.

Because the principles of gas exchange apply to all non-reactive gases, the focus will be mostly on just one gas, O_2. Application to CO_2 will also be indicated but without detailed parallel treatment.

Principles of pulmonary gas exchange

Based on the above, pulmonary gas exchange is considered as a continuous process involving: 1) ventilation, 2) diffusion (including both physical diffusion across the pulmonary blood:gas barrier and

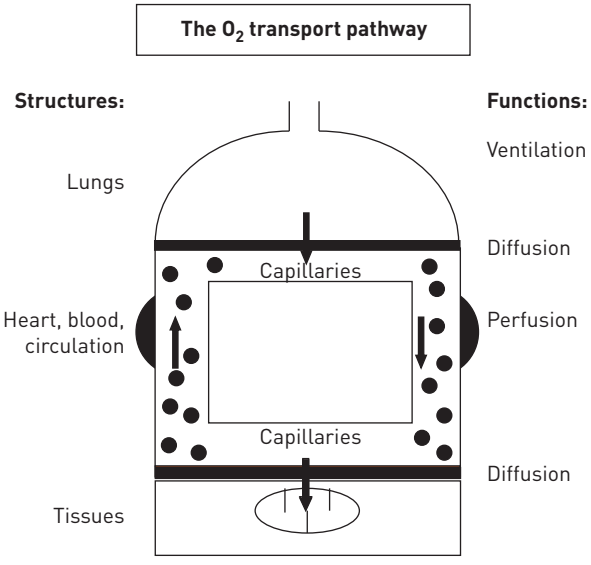

FIGURE 1 Schematic of the O_2 transport pathway showing the principal structures and their physiological functions. The CO_2 transport pathway from the tissues to the lungs mirrors that for O_2.

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subsequent chemical reactions (between O_2 and haemoglobin (Hb) and for CO_2 conversion to bicarbonate), and 3) perfusion. The fundamental principle that brings these three separate physical processes together quantitatively is conservation of mass. All that this means is that within the lungs, every O_2 molecule that is inhaled but not exhaled diffuses from alveolar gas to blood and can be found in that blood.

In quantitative terms, the product of minute ventilation (V'_E, L·min^{-1}) and the difference between inspired and mixed expired O_2 concentrations (F_{IO_2} and F_{EO_2} respectively) quantifies the amount of O_2 (V'_{O_2}) that leaves the alveolar gas and enters the pulmonary capillary blood per minute. The O_2 entering the pulmonary capillaries is quantified by the product of pulmonary blood flow (Q', L·min^{-1}) and the difference between pulmonary venous (C_{pvO_2}) and pulmonary arterial ($C_{\bar{v}O_2}$) O_2 concentrations. In this section, it is assumed, as stated above, that the lungs are homogeneous, such that the concentration of O_2 in the blood leaving every alveolus is the same, and, passing unchanged into the systemic arterial blood, is thus equal to the systemic arterial O_2 concentration (C_{aO_2}). This can now all be expressed by the following simple mass conservation equations:

$$V'_{O_2} = V'_E \times (F_{IO_2} - F_{EO_2}) = V'_A \times (F_{IO_2} - F_{AO_2}) \quad (1)$$

and

$$V'_{O_2} = Q' \times (C_{aO_2} - C_{\bar{v}O_2}) \quad (2)$$

In the right hand part of equation 1, it is recognised that the conducting airways do not themselves take part in air/blood gas exchange. This allows minute ventilation and mixed expired O_2 concentration to be replaced by alveolar ventilation (V'_A) and alveolar O_2 concentration (F_{AO_2}), respectively.

Because the process of diffusional transport described above usually comes to rapid completion well within the red cell transit time (at rest at sea level) [3], the P_{O_2} in the alveolar gas (P_{AO_2}) and the capillary blood leaving the alveolus can be considered to be the same. This means that C_{pvO_2} (and thus C_{aO_2} in equation 2) is that O_2 concentration that can simply be read off the HbO_2 dissociation curve at the value of P_{AO_2} (noting that $P_{AO_2} = F_{AO_2} \times k$, where k is a constant equal to (barometric pressure minus saturated water vapour pressure)/100).

More than 60 years ago, Rahn and Fenn [4] and Riley, Cournand and co-workers [5–7] separately put these equations together noting that both expressed the same variable, V'_{O_2}:

$$V'_A \times (F_{IO_2} - F_{AO_2}) = Q' \times (C_{aO_2} - C_{\bar{v}O_2}) \quad (3)$$

Rearranging the terms gives:

$$V'_A/Q' = 8.63 \times (C_{aO_2} - C_{\bar{v}O_2})/(P_{IO_2} - P_{AO_2}) \quad (4)$$

Here the constant term harmonises the equation when the units used are L·min^{-1} for both V'_A (BTPS) and Q'; mL·dL^{-1} (STPD) for both C_{aO_2} and $C_{\bar{v}O_2}$; and mmHg for both P_{IO_2} and P_{AO_2}.

In the preceding, some simplifying assumptions have been made. We do assume ventilation and perfusion are continuous processes, implying blood and gas O_2 concentrations are constant in time, thus ignoring the normal, minor fluctuations in alveolar P_{O_2} between inspiration and expiration [8]; we have, for now, assumed the lung is homogenous, with all alveoli having the same V'_A/Q' ratio; we have assumed that inspired and expired gas volumes are identical, which is true to within 1%; and we have assumed that the blood leaving the alveoli and entering the pulmonary veins reaches the systemic arteries (where it can be sampled clinically) without change in O_2 concentration—hence the "a" in C_{aO_2} to denote arterial blood. Finally, diffusion equilibration has been assumed as mentioned above, allowing C_{aO_2} to be directly calculated from the HbO_2 dissociation curve, if P_{AO_2} is known. While all theoretically important, these assumptions are a good way to start understanding gas exchange; if they had to be removed, understanding gas exchange would become an intractable exercise in a short article such as this. Research has shown that in health the numerical effect of their combined considerations is mostly trivial, justifying setting them aside. In disease, heterogeneity of V'_A and Q' may be severe and then the assumption of homogeneity is invalid, as discussed below.

Equation 4 is telling us this: if we know 1) the V'_A/Q' ratio in the lung (total alveolar ventilation to total pulmonary blood flow); 2) the composition of inspired gas and pulmonary arterial blood (P_{IO_2} and $C_{\bar{v}O_2}$ in the equation); and 3) the shape and position of the HbO_2 dissociation curve (so we can calculate C_{aO_2}

from P_{AO_2}), then there is but one unknown remaining variable in the equation: P_{AO_2}. In other words, P_{AO_2} is uniquely determined by the V'_A/Q' ratio, given the composition of inspired gas and venous blood and the HbO_2 dissociation curve particulars. The relationship between P_{AO_2} and V'_A/Q' derived by solving equation 4 for homogeneous lungs over a wide range of hypothetical V'_A/Q' ratios is shown in figure 2.

The next step in analysis is that within a given lung, equation 4 can be applied to regions with different V'_A/Q' ratio, and the results shown in figure 2 still apply, but now to each region, according to that region's V'_A/Q' ratio. Also shown in figure 2 are the corresponding results for CO_2. Following through the exact same logic presented for O_2, the equation for CO_2 is:

$$V'_A/Q' = 8.63 \times (C_{\bar{v}CO_2} - C_{aCO_2})/(P_{ACO_2} - P_{ICO_2}) \quad (5)$$

The terms on the right side for CO_2 are reversed (compared to O_2) only because CO_2 is being eliminated from the blood while O_2 is being taken up. This keeps both numerator and denominator for equation 5 positive. The curves in figure 2 are different in shape and slope largely because of the different shapes and slopes of the respective dissociation curves of the two gases, and because O_2 is taken up while CO_2 is eliminated.

Figure 2 is very revealing: When V'_A/Q' is normal (*i.e.* about 1), P_{AO_2} is 100 mmHg and P_{ACO_2} 40 mmHg. If a region of lung becomes poorly ventilated, usually due to airway obstruction, but maintains normal perfusion, V'_A/Q' ratio of that region must be reduced, and P_{AO_2} and blood O_2 concentration will fall (and P_{ACO_2} rise, but by only a small amount). Conversely, as V'_A/Q' rises in a lung region, often due to vascular obstruction, P_{AO_2} rises while P_{ACO_2} falls. Because of the differences in the respective dissociation curves, O_2 concentration rises only little, but P_{ACO_2} and CO_2 concentration fall considerably. This is a profound conclusion: when low V'_A/Q' ratio regions exist, O_2 is seriously affected, more so than CO_2, but when high V'_A/Q' ratio areas develop, CO_2 is the more affected gas.

The alveolar gas equation

The equation for CO_2 corresponding to that for equation 1 for O_2 is now presented:

$$V'_{CO_2} = V'_A \times (F_{ACO_2} - F_{ICO_2}) \quad (6)$$

If equation 6 is simply divided by equation 1, and ignoring F_{ICO_2} as negligible, we get:

$$V'_{CO_2}/V'_{O_2} = R = F_{ACO_2}/(F_{IO_2} - F_{AO_2}) = P_{ACO_2}/(P_{IO_2} - P_{AO_2}) \quad (7)$$

Here R is by definition the respiratory exchange ratio, and the change from fractional concentration (F) to partial pressure (P) follows Dalton's law of partial pressures. If we now rearrange equation 7 we have:

$$P_{AO_2} = P_{IO_2} - P_{ACO_2}/R \quad (8)$$

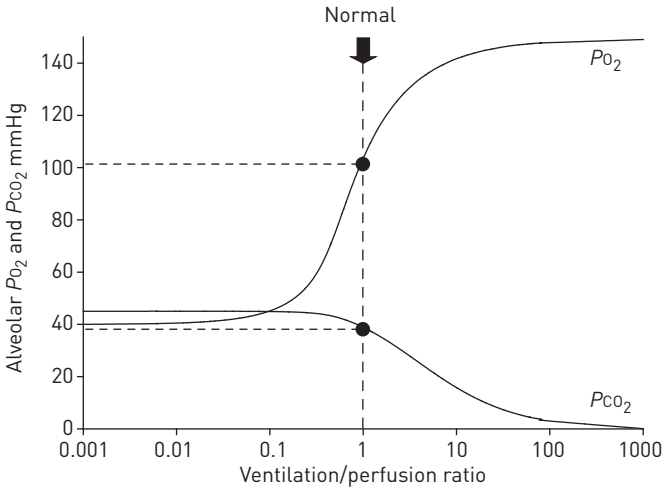

FIGURE 2 Alveolar oxygen and carbon dioxide partial pressures (P_{O_2} and P_{CO_2}) in homogeneous regions having the alveolar ventilation/perfusion ratio indicated on the abscissa. The curves represent the solutions to equations 4 (O_2) and 5 (CO_2).

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This is the simple form of the well-known alveolar gas equation that relates alveolar P_{O_2} to alveolar P_{CO_2}. If one wishes to be accurate and eliminate the assumption that the inspired and expired ventilation values are identical, it can be shown that equation 8 is modified [4]:

$$P_{AO_2} = P_{IO_2} - P_{ACO_2}/R + P_{ACO_2} \times F_{IO_2} \times (1 - R)/R \quad (9)$$

We will return to the application and use of this equation in the last section of this article.

Arterial P_{CO_2} is of course also used, in conjunction with arterial pH, for analysis of blood acid:base balance. That is itself a large and very important topic and will not be addressed in this article, being beyond its scope.

Ventilation/perfusion inequality

Even the normal lung is not homogeneous with respect to ventilation and perfusion of all 300 million alveoli [1, 2]. The amount of inequality can be described by the dispersion of the frequency distribution of V'_A/Q' ratios (called LOG SDQ), a number akin to the standard deviation of a normal distribution [9]. What does heterogeneity do to gas exchange? Inequality in the distribution of V'_A, Q' and V'_A/Q' impairs gas exchange [9]. Figure 3a shows how increasing inequality (*i.e.* dispersion) will affect arterial P_{O_2}, arterial P_{CO_2}, O_2 uptake (V'_{O_2}), CO_2 elimination (V'_{CO_2}) and the alveolar-arterial P_{O_2} difference (P_{A-aO_2}, see below). Arterial P_{O_2} will fall; arterial P_{CO_2} and P_{A-aO_2} will rise (solid lines); V'_{O_2} and V'_{CO_2} will fall (dashed lines), all compared to the perfect lung with no inequality. The calculations shown in the top panel reflect gas exchange before there has been any change in the O_2 and CO_2 levels of the venous blood returning to the lungs. However, as arterial P_{O_2} falls and P_{CO_2} rises, the tissues will immediately continue to extract the O_2 they need and produce the corresponding CO_2. This in turn results in a rapid fall in venous P_{O_2} and rise in venous P_{CO_2}, and this will then cause a further fall in arterial P_{O_2} (and increase in arterial P_{CO_2}). These changes do however allow V'_{O_2} and V'_{CO_2} to be restored to normal, and are shown in figure 3b. The calculations are based on well-established computer algorithms that solve the preceding equations for many different values of V'_A/Q' ratio and sum up their effects according to how much dispersion is introduced [9]. Figure 3 reveals that both O_2 and CO_2 are affected by V'_A/Q' inequality even if the numerical changes are different for the two gases (differences attributable to the different shape and slope of their dissociation curves). The figure also demonstrates the broader principle of how mass transport can be normalised in the face of disease, but at a price. Here, mass transport of O_2 and CO_2 can be restored, the price being more severe hypoxaemia and hypercapnia (comparing figure 3a and b). This is much like the elevation of blood urea in chronic renal failure, where daily urea excretion by the kidney can be maintained, but the cost is a high blood urea level.

It does not matter whether the cause of the increased V'_A/Q' ratio dispersion is regional airway obstruction or regional vascular obstruction: the changes from normal will always be in the same direction. However, if the primary lesion is airway obstruction, O_2 will be affected more than will CO_2, while the reverse holds when vascular obstruction is the primary pathology (as explained above in reference to figure 2).

Compensatory processes

If V'_A/Q' inequality develops from disease, and pulmonary uptake of O_2 (and elimination of CO_2) are reduced as above, the tissues will not be able to sustain metabolic rate and if the problem is severe, death will ensue unless the body finds a way to compensate. It is critical to understand the existence and importance of the three innate compensatory processes available to the organism to enable restoration of O_2 and CO_2 transport between lungs and tissues under such circumstances.

The first process is for the tissues to simply extract more O_2 from the blood they receive to restore O_2 flux. Since V'_A/Q' inequality increases P_{CO_2} in the arterial blood that reaches the tissues, P_{CO_2} in the tissues will increase as CO_2 continues to be produced, and thus the venous P_{CO_2} returning to the lungs will also be higher than normal, again returning CO_2 elimination towards normal. These changes in O_2 and CO_2 are both very rapid, passive, diffusive processes and will occur automatically, before the patient is seen by a clinician. Because blood returns from the tissues with its Hb normally still 75% saturated with O_2, it contains a lot of O_2 that is not normally required, and which can be used to support metabolism. This simple strategy is often very effective. This may well be all that is required to restore V'_{O_2} to normal even as the V'_A/Q' problem remains. The price paid is a more severe drop in arterial P_{O_2}, as one would predict from equation 4 and as shown in figure 3.

The second available process is to increase ventilation (V'_A). As ventilation is increased, V'_A/Q' ratios throughout the lungs will also be raised, raising P_{AO_2} and hence also arterial P_{O_2}. At the same time,

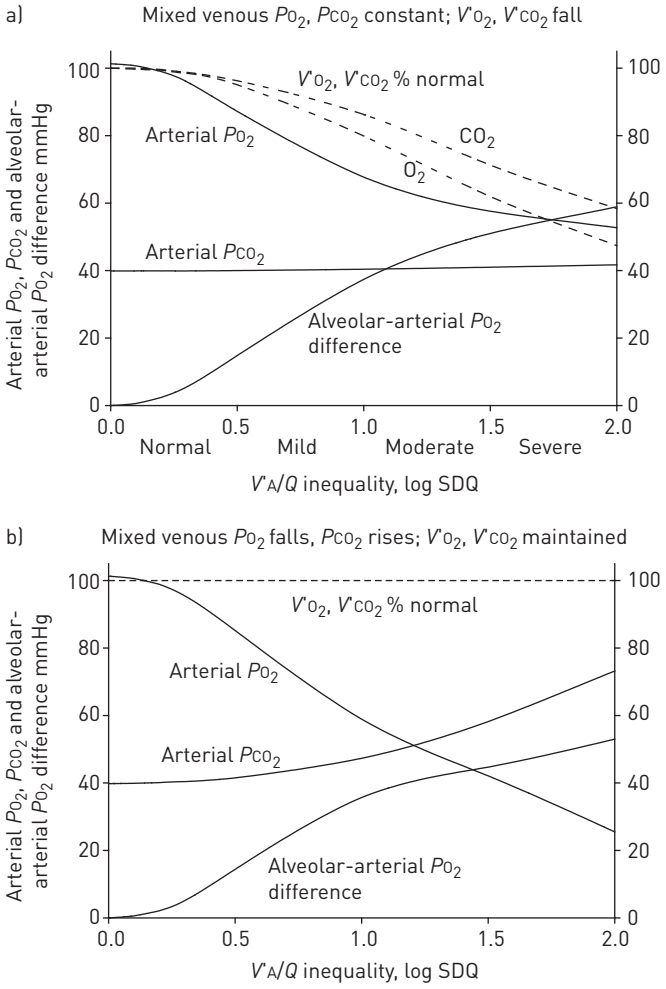

FIGURE 3 Arterial oxygen partial pressure (P_{O_2}) falls and alveolar-arterial P_{O_2} difference rises as the degree of alveolar ventilation/perfusion (V'_A/Q') inequality (LOG SDQ, the second moment of the V'_A/Q' distribution (log scale)) becomes more severe. Normal subjects have LOG SDQ values between 0.3 and 0.6. Patients with chronic obstructive pulmonary disease or asthma will usually have values around 1.0, while patients with acute lung injury in the intensive care unit usually have values between 1.5 and 2.5. a) The effects of V'_A/Q' inequality prior to any fall in mixed venous (pulmonary arterial) P_{O_2} or rise in mixed venous P_{CO_2}: O_2 uptake and CO_2 elimination are reduced. b) The same variables are reflected when mixed venous P_{O_2} falls and P_{CO_2} rises, which normalises O_2 uptake and CO_2 elimination: there is, however, more severe hypoxaemia and hypercapnia as a consequence.

P_{ACO_2}, and thus arterial P_{CO_2}, will be reduced. This compensatory process is also common, and in the absence of airway obstruction, can be very effective. Hyperventilation is especially effective in returning arterial P_{CO_2} to normal (or even subnormal) because of the almost linear shape of the CO_2 dissociation curve. In contrast, it is usually less effective in mitigating the fall in arterial P_{O_2} due to the non-linear shape of the HbO_2 dissociation curve. In patients with airways obstruction (*e.g.* chronic obstructive pulmonary disease (COPD) and asthma) the effect on work of breathing and thus shortness of breath can be considerable, and distressing to the patient. Furthermore, persistent obstruction will not materially raise ventilation, or thus alveolar P_{O_2}, in the alveoli distal to the obstruction, and this combines with the non-linear shape of the O_2 dissociation curve in limiting the gains in arterial P_{O_2} from increased overall ventilation.

The third available process is to increase cardiac output. This mitigates the fall in arterial P_{O_2} because it allows less O_2 extraction in the issues (*i.e.* allows, *via* equation 2, a higher venous O_2 concentration) thereby raising the P_{O_2} in the venous blood returning to the lungs, and as a result, raising arterial P_{O_2}, *via* equation 4. Even if overall and regional ratios of V'_A/Q' fall as a result of the increase in Q', the net result is beneficial to arterial P_{O_2}. In the absence of cardiac disease, this can be an effective compensatory process, and is often observed in younger asthmatics who show sympathetic activation either from anxiety, sympathomimetic drugs, or both. This compensatory tactic will also work to reduce venous P_{CO_2} towards normal which, in turn, helps normalise arterial P_{CO_2}.

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Causes of arterial hypoxaemia and hypercapnia

Armed with all of the above information, we can now lay out the possible causes of a reduction in arterial P_{O_2} (*i.e.* arterial hypoxaemia) and increase in arterial P_{CO_2} (*i.e.* arterial hypercapnia). The statements that follow assume that there have been no compensatory mechanisms brought into play in each case.

1) Reduced inspired P_{O_2} (going to altitude, aircraft travel (where cabin altitudes are commonly equivalent to around 6000–8000 feet). This will not cause hypercapnia; indeed, ventilatory stimulation from hypoxia will reduce arterial P_{CO_2}. However, should inspired P_{CO_2} be increased for any reason, arterial hypercapnia will occur.

2) Overall hypoventilation. This will cause both arterial hypoxaemia and hypercapnia.

3) Ventilation/perfusion (V'_A/Q') inequality. This will cause both arterial hypoxaemia and hypercapnia.

4) Diffusion limitation across the alveolar blood:gas barrier. While a common cause of hypoxaemia in exercise and at altitude even in health, it is uncommon in disease, and to date, diffusion limitation has not been found to affect overall CO_2 exchange.

5) Shunting (the flow of blood from right to left sides of the heart without ever seeing alveolar gas). While often causing profound hypoxaemia, hypercapnia can also occur when shunting is massive.

6) Reduction in pulmonary arterial P_{O_2} (seen when Q' is low in relation to V'_{O_2}). This will cause hypoxaemia in lungs with V'_A/Q' inequality. Correspondingly, an increase in pulmonary arterial P_{CO_2} will cause arterial hypercapnia.

Cause 1: reduced inspired P_{O_2}

With the fall in barometric pressure with altitude, inspired P_{O_2} (P_{IO_2}) falls even as the fractional O_2 concentration remains constant at about 0.21. The alveolar gas equation (equation 8) is very useful for understanding the quantitative consequences, and shows that P_{AO_2} will fall exactly as much as P_{IO_2} as the latter is reduced, if P_{CO_2} and R stay constant. In reality, P_{AO_2} will not decrease as much as P_{IO_2} because of hypoxic ventilatory stimulation. The resulting hyperventilation causes P_{CO_2} to fall and P_{O_2} to rise, as shown in figure 4, reproduced from the 1955 monograph by Rahn and Fenn "A graphical analysis of the respiratory gas exchange" [4]. Normal values for arterial P_{O_2} at altitude need to take hyperventilation, which increases with increasing altitude, into account, and should not simply be estimated as P_{AO_2} in equation 8 assuming P_{CO_2} is unchanged.

An increase in inspired P_{CO_2} will raise alveolar P_{CO_2} at any given value of V'_A/Q' ratio (equation 5), and thus arterial P_{CO_2}. Increased inspired P_{CO_2} is generally not encountered clinically except for accidental exposures, but may be purposefully imposed in research studies.

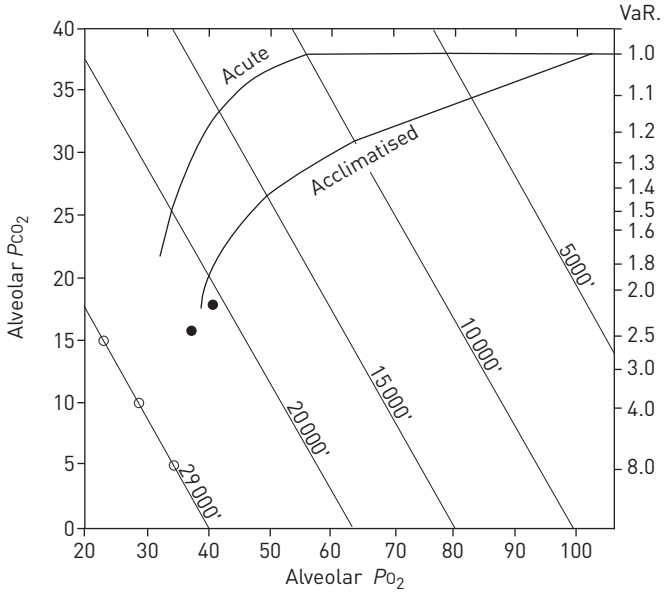

FIGURE 4 Alveolar oxygen and carbon dioxide partial pressures (P_{O_2} and P_{CO_2}) measured in normal subjects with acute and chronic altitude exposure. Hypoxia-driven hyperventilation reduces P_{CO_2} and raises P_{O_2} compared to sea levels values as shown. Reproduced with permission from the publisher [4].

Cause 2: overall hypoventilation

Overall hypoventilation (reduced alveolar ventilation, V'_A) in a patient with normal lungs can occur under many conditions such as after narcotic drug overdose, in states of severe muscle weakness, or in traumatic injury to any portion of the respiratory system. It commonly is accompanied by additional causes of hypoxaemia (especially 3 and 5 below), but will be discussed here assuming it is the only abnormality present. Equations 1 (for O_2) and 6 (for CO_2) show how maintaining metabolic rate in the face of a fall in V'_A has major effects on alveolar P_{O_2} (which falls) and P_{CO_2} (which rises, such that absence of hypercapnia excludes hypoventilation). Figure 5 shows these effects quantitatively. Normal resting alveolar ventilation is about 5 $L \cdot min^{-1}$. The important point is that as V'_A falls even modestly, the effects will be dramatic for both O_2 and CO_2. Because in this example the lungs are assumed to remain normal, the alveolar arterial difference calculated from the alveolar gas equation (equation 8) remains normal.

Cause 3: ventilation/perfusion inequality

V'_A/Q' inequality occurs normally, but this is of minimal clinical importance as a cause of arterial hypoxaemia: arterial P_{O_2} (at sea level) is usually above 90 mmHg in normal subjects. However, in cardiopulmonary diseases, V'_A/Q' inequality can be severe, and lead to very low arterial P_{O_2} values (fig. 3). It may be severe enough to be fatal. Essentially all lung diseases cause significant V'_A/Q' inequality, although the physiological and structural mechanisms can be extremely variable from disease to disease. Inequality affects P_{O_2} no matter whether the primary pathology resides in the blood vessels, the parenchymal tissues, or the airways.

It is very important to recognise that V'_A/Q' inequality impairs the exchange of all gases, not just that of O_2. Thus, in addition to hypoxaemia, arterial hypercapnia will always be an initial result of V'_A/Q' inequality. That said, when arterial blood gases are measured in patients with V'_A/Q' inequality, arterial P_{CO_2} may be normal or even below normal. This apparent contradiction is easily understood if the degree of compensatory hyperventilation (see above) is taken into account. Because of differences in the shapes and slopes of their dissociation curves, O_2 and CO_2 tensions in blood will respond quite differently to both the initial V'_A/Q' inequality and to subsequent ventilatory compensation. Arterial P_{O_2} usually falls much more than does P_{CO_2} rise when V'_A/Q' inequality develops. In addition, arterial P_{CO_2} is often normalised by even small compensatory increases in ventilation, but this is not the case for O_2, where the increase in P_{O_2} is usually more modest. As a result, V'_A/Q' inequality essentially always results in hypoxaemia, although arterial P_{CO_2} can be high, normal or low, depending on the amount of compensatory hyperventilation.

A final important point about V'_A/Q' inequality is that while it causes significant hypoxaemia breathing room air, arterial P_{O_2} increases to levels seen in normal subjects when 100% O_2 is breathed. This is because, given enough time (it may take 10–30 min), 100% O_2 breathing washes out all alveolar nitrogen, leaving only O_2 and CO_2 in the alveolar gas. This means that even in poorly ventilated regions, alveolar P_{O_2} will rise to above 600 mmHg, just as in normally ventilated regions.

Cause 4: diffusion limitation

As stated, all gases exchange between alveolar gas and pulmonary capillary blood by passive diffusion. Factors that affect the diffusional conductance of a gas include the thickness of the blood:gas barrier, the overall alveolar–capillary contact surface area, the solubility of the gas in the haemoglobin-free blood:gas

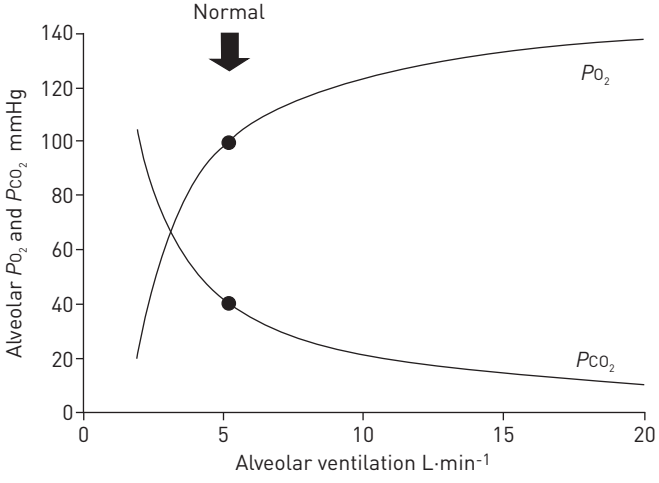

FIGURE 5 Alveolar partial pressure of oxygen (P_{O_2}) (from solving equation 1) and P_{CO_2} (from equation 6) as a function of alveolar ventilation in a normal lung. Note how sensitive both P_{O_2} and P_{CO_2} are to small decreases in ventilation.

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barrier, and the molecular weight of the gas. Additional factors that affect the completeness with which diffusion equilibration occurs in the alveolar microcirculation include the rate of reaction between the gas and haemoglobin (for gases such as O_2, CO and CO_2), the capacity of haemoglobin to carry the gas, and the time a red cell spends in the pulmonary microcirculation exchanging gas. This transit time in turn reflects the ratio of microcirculatory blood volume to blood flow.

This multitude of contributing factors can be brought into a single unifying concept, as shown by PIIPER and SCHEID [10] several years ago. The degree of diffusion equilibration (that is, how close to alveolar partial pressure the blood partial pressure comes by the end of the capillary transit) depends on the ratio of diffusing capacity (D_L) to the product of blood flow (Q') and β; that is, to $D_L/(\beta Q')$. Here, β is the overall "solubility" of the gas in blood. For O_2 it is approximated by the ratio of arterial−mixed venous O_2 concentration difference to arterial−mixed venous P_{O_2} difference, which indicates the average slope of the O_2 dissociation curve. This compound number intrinsically incorporates transit time and capillary volume, as can be seen when one writes down and solves the diffusion equation [10].

In health, at rest at sea level, the red cell requires only about 0.25 s for equilibration—that is, for red cell P_{O_2} to rise from pulmonary arterial to alveolar values [3]. The available transit time is about 0.75 s, implying a three-fold reserve in time available. Failure of equilibration is, therefore, not seen in healthy subjects at rest, and this remains so at rest even at altitude. However, during exercise at sea level, failure of equilibration is frequently (but not universally) observed, especially in athletes who have high rates of blood flow and thus lower red cell transit times. At altitude, exercise results in failure of equilibration in essentially everyone [11]. This is due to the reduced P_{O_2} diffusion gradient stemming from inspiratory hypoxia, especially combined with reduced transit time [12].

In lung diseases, failure of diffusional equilibration is rarely seen. It appears to be consistently measureable only in patients with interstitial lung diseases [13] and is seen most often when they exercise. It is seen at rest only in severe cases of interstitial lung disease when lung function is at 50% of normal or less. It may be a factor contributing to the hypoxaemia in rarer conditions associated with pulmonary arterio-venous malformations and/or vascular dilatation, the most common of which may be cirrhosis of the liver. Here the possibility is that the long intravascular distances O_2 must travel to reach all flowing red cells prevent complete diffusion equilibration within the red cell transit time. The reader is referred to the review by RODRIGUEZ-ROISIN and KROWKA [14] for a more detailed discussion of this topic. It has not been found to happen in COPD [15], asthma [16], pulmonary thromboembolic disease [17] or in the critically ill.

Diffusion limitation of CO_2 has not so far been documented. The diffusing capacity of CO_2 across the blood:gas barrier (quantity of CO_2 transported per minute per mmHg partial pressure difference across that barrier) is much greater than for O_2. This is because of the approximately 20-fold greater physical solubility of CO_2 in the blood gas barrier. However, the capacity of the blood to hold CO_2 (as bicarbonate, dissolved CO_2 and carbamino-Hb), per mmHg P_{CO_2}, is approximately 10-fold greater than that of blood to hold O_2 (per mmHg P_{O_2}). This acts to partly counterbalance the higher barrier solubility just mentioned such that the time to equilibration for CO_2 is not 20 times less than for O_2 but more like only two-fold less. Even considering that the chemical reaction steps whereby CO_2 is converted to bicarbonate inside the red cell, followed by exchange of bicarbonate for chloride, are relatively slow (half-time calculated to be about 0.1 s), CO_2 appears to equilibrate faster than does O_2.

Cause 5: shunting

Shunting is defined as blood passing from right to left sides of the heart without ever seeing alveolar gas. This can be through cardiac shunts (atrial, ventricular), in congenital heart diseases, and in lung diseases associated with atelectasis or alveolar filling with fluid or cell debris. It may also occur in lung diseases associated with large arterio-venous connections, such as cirrhosis and hereditary haemorrhagic telangiectasia [14]. Research has shown that most patients with chronic lung diseases such as COPD and asthma have little if any shunting [15, 16], but that patients with acute lung diseases (pneumonias, acute lung injury, respiratory distress syndromes) typically do have shunts, that can sometimes be severe [18, 19].

Arterial P_{O_2} is usually not very responsive to increases in F_{IO_2} in such patients (in contrast to what is seen with V'_A/Q' inequality, see above). Thus, shunting is best quantified while the patient breathes 100% O_2 in order to eliminate contributions from, and confusion with, V'_A/Q' inequality that usually co-exists with shunting, and diffusion limitation, if present.

While the effects of shunting on arterial P_{O_2} are dramatic and well-known, shunting can also affect arterial P_{CO_2} (and, as mentioned in the introduction, the exchange of all gases). Arterial P_{CO_2} will increase when shunts develop (unless compensated by hyperventilation as commonly occurs). This is because shunted blood, carrying CO_2 at high pulmonary arterial levels, mixes with non-shunted blood to form systemic

arterial blood. Small to moderate shunts of 20% or less raise arterial P_{CO_2} by only a mmHg or two, but the relationship between shunt fraction and arterial P_{CO_2} is quite nonlinear, and when shunt is very high, 40–50% of the cardiac output, arterial P_{CO_2} can rise by more than 10 mmHg (again, in the absence of ventilatory compensation).

Cause 6: reduction in pulmonary arterial P_{O_2} ($P_{\bar{v}O_2}$)

This factor was mentioned above in discussing cardiac output as a potential compensating factor reversing arterial hypoxaemia. At the outset it should be mentioned that there is an exception to the rule that a fall in $P_{\bar{v}O_2}$ will cause a fall in arterial P_{O_2}: the perfectly homogeneous lung. In this case, P_{AO_2} is governed by having to fulfil the conditions of equation 1 above, making it dependent only on V'_{O_2}, V'_A and F_{IO_2} (and thus not on $P_{\bar{v}O_2}$). Because the lung is homogeneous, P_{aO_2} must equal P_{AO_2} and is thus also unaffected by changes in $P_{\bar{v}O_2}$. Reduction in pulmonary arterial P_{O_2} may however better be thought of as an extrapulmonary modifier of arterial P_{O_2}. It comes into play when Q' is low in relation to V'_{O_2} (equation 2), thereby reducing $P_{\bar{v}O_2}$. Its effect is evident from equation 4. Thus, if $P_{\bar{v}O_2}$ falls, so too will P_{AO_2}, and thus arterial P_{O_2} will also fall. Figure 3, described earlier, exemplifies this effect (compare P_{aO_2} between figure 3a and b), and further shows the effects are greater the more V'_A/Q' inequality there is. It is especially important to understand this cause in the critically ill patient receiving inspired gas high in O_2. Arterial P_{O_2} in such a patient may change considerably without change in lung function (causes 2–5 above) or in P_{IO_2} (cause 1 above) if cardiac output changes in relation to metabolic rate. This is shown in figure 6. Distinguishing the causes of change in arterial P_{O_2} is of obvious therapeutic importance in such circumstances.

In a corresponding manner, if Q' is low in relation to V'_{CO_2}, pulmonary arterial P_{CO_2} must rise, and in the face of unchanged ventilation, must cause alveolar and thus arterial P_{CO_2} to increase.

Importantly, many of the above causes may coexist in a given patient, which can result in complex blood gas presentations that can be difficult to unravel in the clinical setting, especially when limited measurements are made.

Assessment and interpretation of arterial blood gases

An orderly, systematic, multi-level approach is recommended, based on the preceding physiological discussion, perhaps as laid out below. Just how detailed one needs to get (how many levels to pursue) will depend on the clinical questions at hand; one should ask for what purpose was the blood gas sample obtained? What was the clinical question that needs to be answered? The suggested system is a physiologically based construct, and is not designed to provide pathogenetic diagnosis of any particular disease state. In other words, it is limited to providing quantitative assessment of the severity of gas exchange disturbances, and the physiological factors underlying them. The levels proceed from the simplest to more complex, and, past level 1, require either additional measurements or making assumptions that may or may not be valid in any given situation. As stated previously, the acid/base component of arterial blood gas analysis (involving pH–P_{CO_2} relationships) is beyond the scope of this article and is not addressed.

The minimal requirement is an arterial blood gas sample in which the P_{O_2}, P_{CO_2}, pH, haemoglobin level and O_2 saturation have been measured, although additional measurements will be necessary for some of the derived indices described below (indicated in the appropriate sections).

Level 1: simply look at the absolute values of arterial P_{O_2}, P_{CO_2}, and pH compared to normal (allowing for the altitude at which measurements are made and age of the patient, which affect the normal range). Allowance for altitude can be performed by use of the alveolar gas equation (equation 8), first by inserting the correct inspired P_{O_2} (P_{IO_2}) value for the particular altitude, and then inserting the actual arterial P_{CO_2} of the patient). In the critically ill breathing gas higher than 21% in O_2, analysis may include dividing arterial P_{O_2} by inspired O_2 concentration (to yield the P_{aO_2}/F_{IO_2} ratio). This is an attempt to correct for F_{IO_2} and is discussed below. Body temperature correction of all numbers should be performed before interpretation. Blood gas electrodes are almost always maintained and calibrated at 37°C, and if a patient is febrile, *in vivo* P_{O_2} and P_{CO_2} will be higher than the reported values measured at 37°C, and *vice versa* if the patient is hypothermic. Most analysers have inbuilt algorithms that correct for temperature automatically if the patient's temperature is entered, and it is these corrected values that should be used for interpretation, and especially in the alveolar gas equation for calculation of the P_{A-aO_2} difference.

The outcomes of this level of analysis are simply to know whether P_{O_2} is within the normal range (accounting for age, altitude, F_{IO_2} and temperature), and similarly if P_{CO_2} is low (<35 mmHg); normal (35–45 mmHg); or high (>45 mmHg). Figures 7 and 8 show how arterial P_{O_2} and the P_{aO_2}/F_{IO_2} ratio behave over a range of values of F_{IO_2} and with differing degrees of V'_A/Q' inequality (fig. 7) and shunt (fig. 8). Note that while the two figures do differ systematically from each other, they show complexity such that major simplifications are difficult to achieve. They do show that mapping the variables over

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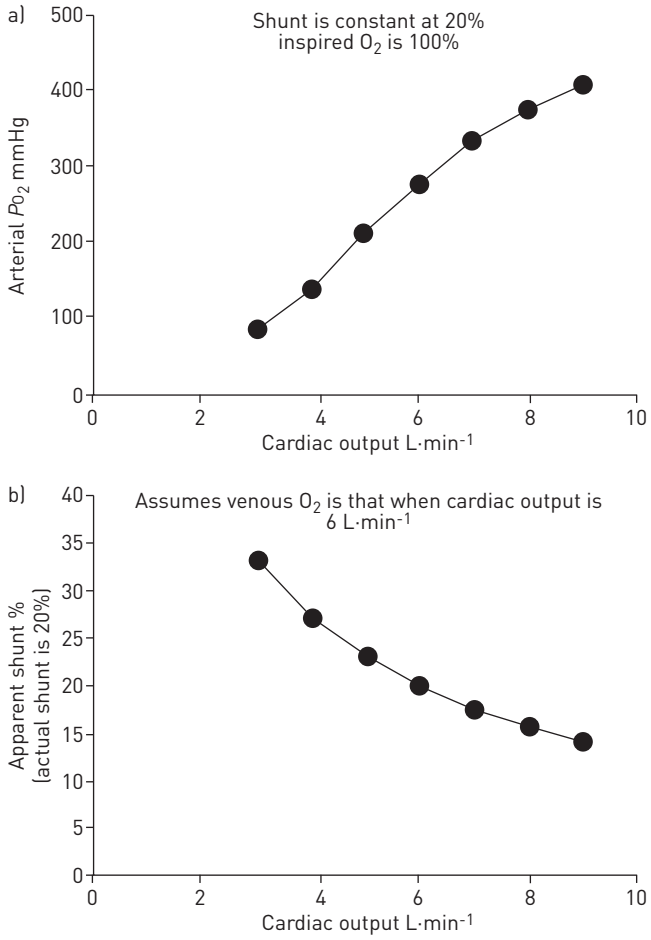

FIGURE 6 Simulation of a patient with a constant shunt of 20% of the cardiac output who is breathing 100% O_2. a) Arterial partial pressure of oxygen (P_{O_2}) is very sensitive to cardiac output because as the latter falls, so must pulmonary arterial P_{O_2} (perfusing the shunt pathway). This highlights the importance of accounting for differences in cardiac output from normal (here taken as 6 L·min^{-1}). b) Apparent shunt computed in the same simulation from equation 11 based on arterial P_{O_2} values in panel a when cardiac output is not normal (but is assumed to be normal). The true shunt may thus be over- or under-estimated considerably.

a range of F_{IO_2} may be helpful in gaining a better understanding of the pathophysiology in individual patients, but this requires labour-intensive repeated arterial blood gas measurements at each F_{IO_2} selected [20].

Level 2: calculate P_{A-aO_2} from the alveolar gas equation (*i.e.* equation 8), using the measured arterial P_{CO_2} (P_{aCO_2}) in place of alveolar P_{CO_2} (P_{ACO_2}), and the respiratory exchange ratio (R). If R is not measured, a reasonable value of 0.80–0.85 can be assumed, but differences between assumed and actual R values can induce substantial errors in the P_{A-aO_2} as the equation implies. For example, at normal arterial P_{CO_2} (40 mmHg) and R = 0.8, P_{AO_2} would be 99 mmHg (room air, sea level). However, if R were 0.7, P_{AO_2} would be 92 mmHg, and if R=1, P_{AO_2} would be 109 mmHg.

Equation 8 yields the alveolar P_{O_2} value, and all that needs to be done is to subtract the measured arterial P_{O_2} to give P_{A-aO_2}. In clinical circumstances, the exact form of the alveolar gas equation 9 is not necessary because the additional term in equation 9 is small, as substitution of normal values of P_{aCO_2} and R in to equations 8 and 9 will show.

Breathing room air, P_{A-aO_2} is usually 5–10 mmHg in young healthy subjects, but it increases a little with age to up to 20 mmHg or so [21, 22]. Unfortunately, P_{A-aO_2} is a noisy variable because it represents the usually small difference between two large numbers (alveolar and arterial P_{O_2}). Also, recall that it is based on steady state assumptions, as mentioned earlier, and so in a patient whose condition is rapidly changing, P_{A-aO_2} will not be reliable.

What P_{A-aO_2} provides over and above P_{O_2} and P_{CO_2} from level 1 analysis is the power to discriminate amongst some of the causes of hypoxaemia. Thus, if P_{A-aO_2} is normal yet there is hypoxaemia, one of the

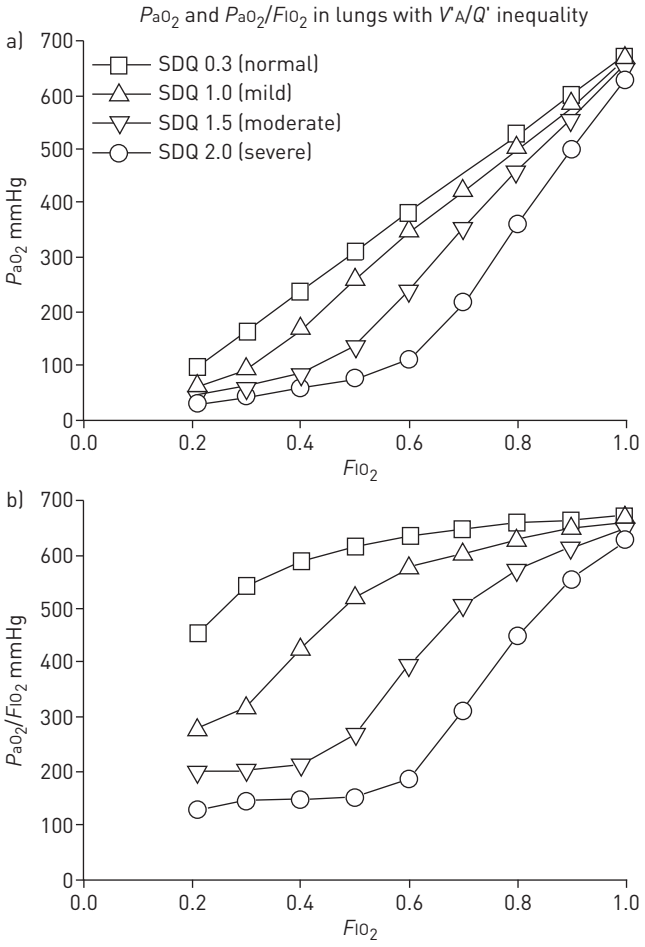

FIGURE 7 a) Arterial partial oxygen pressure (P_{aO_2}) and b) P_{aO_2}/inspired oxygen fraction (F_{IO_2}) ratio as a function of F_{IO_2} in lungs simulated to have only alveolar ventilation/perfusion (V'_A/Q') inequality and no shunt. Note that with moderate to severe inequality, P_{aO_2}/F_{IO_2} is far from constant as F_{IO_2} changes.

first two causes (reduced P_{IO_2}, hypoventilation, respectively) must be the explanation for the reduced arterial P_{O_2}. Distinguishing between the first two causes should be self-evident from knowing F_{IO_2} and examining arterial P_{CO_2}, which is always elevated in cause 2, and usually reduced in cause 1.

Examples are shown in figure 9a (for V'_A/Q' inequality) and figure 10a (for shunt).

Level 3: calculate the physiological shunt (Q_S/Q_T) and the physiological deadspace (V_D/V_T), both defined below.

Q_S/Q_T is a simple calculation that yields the percentage of total blood flow through the lungs that would have to be shunted (see shunt definition above) to explain the measured arterial P_{O_2} on the assumption that the lungs can be simplified to a two-compartment system: one made up of alveoli that are all normally ventilated and perfused, and one that is perfused but not ventilated at all. The calculation uses mass conservation as follows:

$$C_{aO_2} \times Q'_T = C_{iO_2} \times (Q'_T - Q'_S) + C_{\bar{v}O_2} \times Q'_S \quad (10)$$

Where Q'_T is total pulmonary blood flow, Q'_S is that portion of total flow passing through the vessels of the unventilated compartment (whose emerging blood O_2 concentration remains that of the inflowing pulmonary arterial blood, $C_{\bar{v}O_2}$), C_{aO_2} is measured arterial O_2 concentration, and C_{iO_2} is the O_2 concentration calculated, using the HbO_2 dissociation curve, from the "ideal" P_{O_2} or, in essence, the alveolar P_{O_2} determined from equation 8. Rearranging, we get:

$$Q_S/Q_T(\text{as a } \%) = 100 \times (C_{iO_2} - C_{aO_2})/(C_{iO_2} - C_{\bar{v}O_2}) \quad (11)$$

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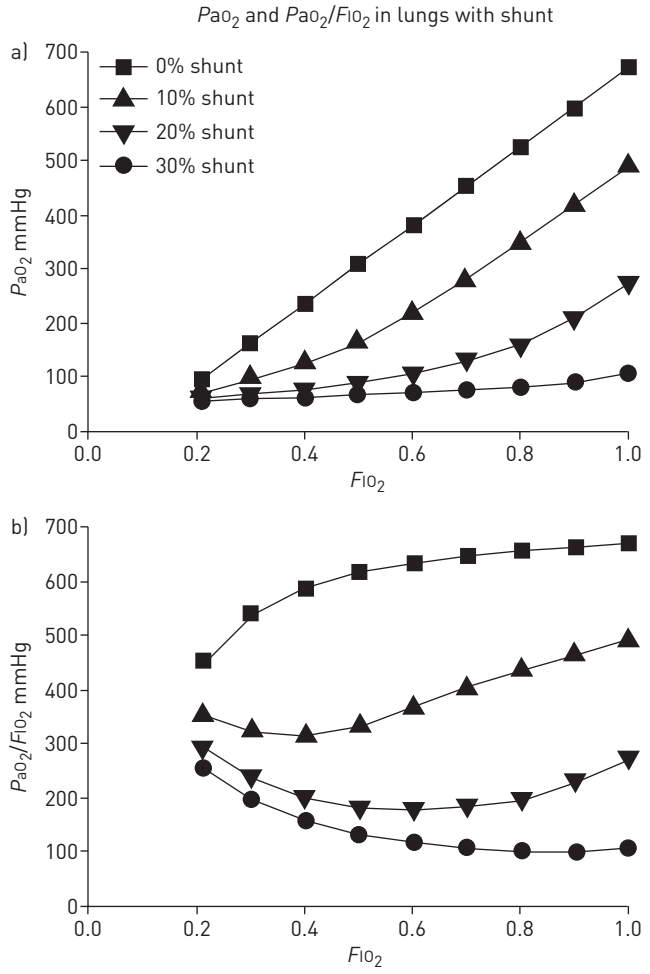

FIGURE 8 a) Arterial partial oxygen pressure (P_{aO_2}) and b) P_{aO_2}/inspired oxygen fraction (F_{IO_2}) ratio as a function of F_{IO_2} in lungs simulated to have only shunt and no alveolar ventilation/perfusion ratio inequality. P_{aO_2}/F_{IO_2} steadily increases with F_{IO_2} when shunt is absent or small, falls and then rises with F_{IO_2} when shunt is moderate, and steadily falls when shunt is large.

Another form of this equation is:

$$Q_S/Q_T = 100 \times (C_{iO_2} - C_{aO_2})/((C_{iO_2} - C_{aO_2}) + (C_{aO_2} - C_{vO_2}))$$

Which from equation (2) can be rewritten as:

$$Q_S/Q_T = 100 \times (C_{iO_2} - C_{aO_2})/((C_{iO_2} - C_{aO_2}) + (0.1 \times V'_{O_2}/Q'_T)) \quad (12)$$

Where C_{iO_2}, C_{aO_2} and C_{vO_2} are all in mL·dL^{-1}, V'_{O_2} is in mL·min^{-1} and Q'_T is in L·min^{-1}. You will have to compute C_{iO_2} and C_{aO_2} from measured arterial blood gas values and saturation as follows:

C_{iO_2} = 1.39 × [Hb] × fractional O_2 saturation (calculated for the value of P_{AO_2}) + 0.003 × P_{AO_2}

C_{aO_2} = 1.39 × [Hb] × fractional O_2 saturation (measured in arterial blood) + 0.003 × P_{aO_2}

Whether you choose to use equation 11 or equation 12 depends on whether you know $C\bar{v}O_2$ or alternatively V'_{O_2} and Q'_T. If you know none of these variables, they will have to be assumed, which will result in uncertainty in the derived value of Q_S/Q_T [23].

The outcome, Q_S/Q_T, quantifies what may be called the virtual shunt. It is also called the physiological shunt, or sometimes, the venous admixture. At ambient F_{IO_2}, most commonly that of sea level room air, Q_S/Q_T may contain contributions from causes 3–6 when present: ventilation/perfusion inequality, diffusion limitation, and shunting plus the modulating effects of changes in the V'_{O_2}/Q'_T relationship if present. It is not possible to separate these potential contributors just from looking at Q_S/Q_T itself, but the

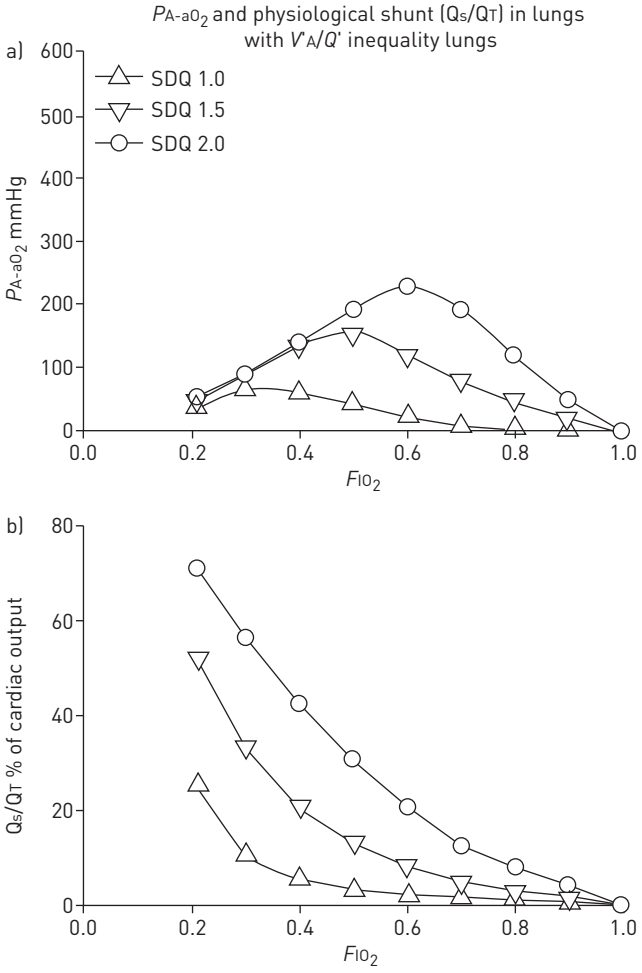

FIGURE 9 a) Alveolar-arterial oxygen partial pressure difference (P_{A-aO_2}) and b) physiological shunt (Q_S/Q_T) as a function of inspired oxygen fraction (F_{IO_2}) in lungs simulated to have only alveolar ventilation/perfusion (V'_A/Q') inequality and no shunt. P_{A-aO_2} peaks at intermediate F_{IO_2} while physiological shunt steadily falls with increasing F_{IO_2} in spite of constant amounts of inequality.

number obtained is a good overall index of the total gas exchange defect at the F_{IO_2} experienced by the patient. Its utility beyond that of P_{A-aO_2} is to quantify the gas exchange problem in terms of O_2 concentration rather than partial pressure. O_2 concentration is a better indicator of the effect on mass transport than is partial pressure, due to the nonlinear nature of the HbO_2 dissociation curve. Q_S/Q_T will not normally exceed 5% of the cardiac output from all causes combined.

Examples are shown in figure 9b (for V'_A/Q' inequality) and figure 10b (for shunt).

V_D/V_T (physiological deadspace) is exactly analogous (and complementary) to Q_S/Q_T as follows. It represents a hypothetical CO_2-free fraction of the total minute ventilation (V'_E, equation 1) that would have to be added to alveolar gas having a P_{CO_2} equal to that measured in arterial blood in order to reach the measured P_{CO_2} in mixed expired gas. Since the conducting airways (known as the deadspace) do not contribute to gas exchange, that CO_2-free fraction is thought of as deadspace. The equation is as follows, very similar to that for Q_S/Q_T as it is also based on a two-compartment construct:

$$V'_E \times P_{ECO_2} = (V'_E - V'_D) \times P_{aCO_2} + V'_D \times \text{zero} \quad (13)$$

Where P_{ECO_2} is the P_{CO_2} measured in mixed expired gas, P_{aCO_2} is arterial P_{CO_2}, V'_E ($L \cdot min^{-1}$) is minute ventilation, and V'_D ($L \cdot min^{-1}$) is the ventilation associated with the virtual deadspace compartment (P_{CO_2} of zero). Rearranging equation 13 and multiplying by 100 to give the result as a percentage yields:

$$V'_D/V'_E = 100 \times (P_{aCO_2} - P_{ECO_2})/P_{aCO_2} \quad (14)$$

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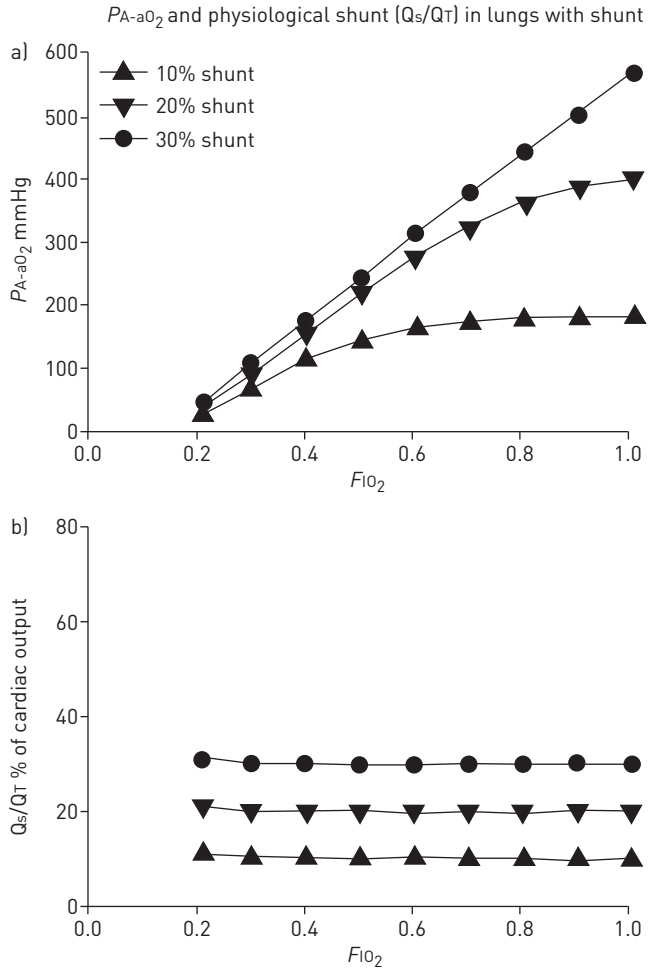

FIGURE 10 a) Alveolar-arterial oxygen partial pressure difference (P_{A-aO_2}) and b) physiological shunt (Q_S/Q_T) as a function of inspired oxygen fraction (F_{IO_2}) in lungs simulated to have only shunt and no alveolar ventilation/perfusion inequality. Arterial P_{O_2} steadily rises but calculated shunt remains constant as F_{IO_2} is raised.

More commonly, V'_E is renamed V_T in this equation, yielding the familiar term "V_D/V_T". Unlike Q_S/Q_T, the normal value of which is near zero, the absence of gas exchange in the 17 or so generations of the conducting airways of the lung (airways which total about 150 mL in volume) [24] contribute substantially to V_D/V_T. The tidal volume (volume of each breath) is about 500 mL at rest, and so V_D/V_T is normally 150/500 or 30%. Unfortunately, changes in tidal volume will have a major effect on V_D/V_T. If a subject dropped tidal volume to 400 mL, V_D/V_T would now become 150/400 or 38%. An exercising subject with a 2 L tidal volume will have a V_D/V_T of 150/2000, or just 8%.

It is therefore recommended to multiply V_D/V_T by actual tidal volume and estimate V_D in mL per breath, which normally should approximate 150 mL, whatever the tidal volume. Then, any increase in V_D above 150 mL per breath (*i.e.* $V_D - 150$) likely denotes an alveolar gas exchange abnormality typified by development of areas of increased V'_A/Q' ratio. Any such increase in V_D is interpreted as a virtual defect; alveoli considered as being ventilated but not perfused, with a volume per breath equal to V_D (as measured) less 150 mL. It should also be remembered that the volume of the conducting airways (150 mL in the preceding) varies with body size, and using 2 mL·kg^{-1} in subjects with normal BMI is reasonable [25]. In very obese subjects, one should probably use 2 mL·kg^{-1} lean body mass.

Note that in addition to the arterial blood gas measurement of P_{CO_2}, one needs to collect and measure P_{CO_2} in mixed expired gas (P_{ECO_2}), and measure tidal volume (either directly or by measuring V'_E and dividing by respiratory frequency). Sometimes, the end-tidal P_{CO_2} is measured rather than the arterial, with the assumption that they are the same. This is reasonable in health but may be quite incorrect in disease, where end-tidal P_{CO_2} may exceed arterial P_{CO_2}, due to 1) continuing addition of CO_2 to alveolar gas during expiration, and 2) more poorly ventilated regions with higher than average P_{CO_2} emptying later in each breath. Finally, the mixed expired P_{CO_2} can be computed from rapid analysis of exhaled CO_2

during a single breath (avoiding the task of manually collecting expired gas and measuring its P_{CO_2}), but for this, one needs a rapid CO_2 analyser connected to a computer and associated software.

Level 4: intervention with 100% O_2 to determine the amount of shunting distinct from other factors contributing to hypoxaemia. The same equations (11 or 12) are used as for $\dot{Q}_S/\dot{Q}_T$, and the concept is very similar. The only real difference is that in level 3, ambient F_{IO_2} is used, while here one intervenes by having the patient breathe 100% O_2. If the patient is breathing pure O_2, real shunting is the only cause of hypoxaemia contributing to $\dot{Q}_S/\dot{Q}_T$. The value is normally zero, since significant shunting does not occur in normal lungs [1, 26], but due to (random) errors, the calculation may reveal a value of perhaps 2–3%. Of interest, Thebesian venous drainage directly into the cavity of the left ventricle should add poorly saturated venous blood to arterial and act as a shunt. Based on studies using the multiple inert gas elimination technique [1], such shunting has never been observed, implying that its contribution to lowering arterial P_{O_2} is very small. Usually, the resulting value of $\dot{Q}_S/\dot{Q}_T$ on 100% O_2 is less than that measured at lower F_{IO_2}, because contributions from $\dot{V}'_A/\dot{Q}'$ inequality and diffusion limitation are eliminated as explained above.

To use this procedure with accuracy, the arterial blood sample should be processed realising that most errors cause the reported P_{O_2} to be lower than it really was in the sample when collected. Small air bubbles in the sampling syringe, continuing metabolic use of O_2 by white cells in the sample, air contamination during measurement and O_2 consumption by the blood gas electrodes themselves during measurement all pull the P_{O_2} down. Using bubble-free syringes, keeping the sample iced and making the measurement as quickly as possible, are all key to accurate measurement.

The extreme right hand points in figures 7–10 show how breathing 100% O_2 affects indices of arterial oxygenation.

Level 5: assessment of extrapulmonary modifying factors: $\dot{V}'_{O_2}$, cardiac output ($\dot{Q}'_T$), Hb concentration, temperature, Hb P50, pulmonary arterial P_{O_2}. These ancillary measurements are intended to help determine when cause 6 is an important contributor to the level of hypoxaemia. Quick guides are that if the ratio of $\dot{V}'_{O_2}$ ($mL \cdot min^{-1}$) to $\dot{Q}'_T$ ($L \cdot min^{-1}$) exceeds 50, the value of $P_{\bar{v}O_2}$ would be expected to be lower than normal and contribute to the hypoxaemia over and above the other five causes. An important exclusion to this effect of a low $P_{\bar{v}O_2}$ on arterial P_{O_2} is when the lungs have no $\dot{V}'_A/\dot{Q}'$ inequality or diffusion limitation at all. In this case, all alveoli have the same P_{O_2} (alveolar and end-capillary) that is determined, as can be seen by examining equation 1, only by metabolic rate ($\dot{V}'_{O_2}$), alveolar ventilation ($\dot{V}'_A$) and inspired O_2 fraction (F_{IO_2}). The effect becomes greater with increasing amounts of $\dot{V}'_A/\dot{Q}'$ inequality. In health, the amount of inequality is sufficiently small that a low $P_{\bar{v}O_2}$ hardly affects arterial P_{O_2}.

Figure 6 exemplifies the degree to which this may affect arterial P_{O_2} and the shunt calculation. The effects may be considerable. Also, if Hb concentration is very low, $P_{\bar{v}O_2}$ will be lower than usual. Contributions from alterations in P50 and temperature are generally clinically small and moreover difficult to estimate, although P_{O_2} and P_{CO_2} in blood increase about 6–7% per °C change in temperature [27].

TABLE 1 Separation of physiological causes of hypoxaemia

Cause of hypoxaemia	Typical example	Arterial P_{CO_2}	P_{A-aO_2} difference	Arterial P_{O_2} on 100% O_2 and $\dot{Q}_S/\dot{Q}_T$	$\dot{V}'_{O_2}/\dot{Q}'$ ratio
Low inspired P_{O_2}	Altitude	↓	Normal	Normal (for altitude)	Normal or ↓
Hypoventilation	Narcotic overdose	↑	Normal	Normal	Normal
$\dot{V}'_A/\dot{Q}'$ inequality	Most lung diseases	↑ or normal or ↓	↑	Normal	Normal
Diffusion limitation	Exercise at altitude; interstitial fibrosis	Normal	↑	Normal	Normal
Shunts	Acute lung injury	↑ or normal or ↓	↑	P_{O_2} below normal; $\dot{Q}_S/\dot{Q}_T$ increased	↑ or normal or ↓
Extrapulmonary: high $\dot{V}'_{O_2}/\dot{Q}'$ ratio (with lung disease)	Heart failure with pulmonary oedema or lung disease	↑ or normal or ↓	↑	Normal (if no shunt)	↑
Cautionary notes		Highly dependent on individual ventilatory responsiveness	Accuracy requires R ($\dot{V}'_{CO_2}/\dot{V}'_{O_2}$) to be known	Potentially large errors if $P_{\bar{v}O_2}$ is unknown; risk of measurement error in arterial P_{O_2}	Requires $\dot{V}'_{O_2}$ and $\dot{Q}'$ to be measured

P_{CO_2}: carbon dioxide partial pressure; P_{O_2}: oxygen partial pressure; P_{A-aO_2}: alveolar–arterial P_{O_2} difference; $\dot{Q}_S/\dot{Q}_T$: shunt; $\dot{V}'_{O_2}$: oxygen uptake; $\dot{Q}'$: perfusion; $\dot{V}'_A$: alveolar ventilation; $\dot{V}'_{CO_2}$: carbon dioxide elimination; $P_{\bar{v}O_2}$: pulmonary arterial P_{O_2}.

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Table 1 brings all of these concepts together in summary form. It is wise to remember, however, that summary tables, such as this, depict usual or common situations, and that to every rule there can be an exception. In particular, the interaction between any of the listed causes of hypoxaemia and ventilatory responsiveness of the subject plays a large role in the blood gas picture seen in an individual, explaining why the arterial P_{CO_2} can be elevated, reduced or normal in many settings.

Summary

While gas exchange in the lungs follows straightforward principles which are well understood, assessment of the severity and nature of gas exchange disturbances in patients can be complicated, and in particular, requires not just arterial blood gas data, but a defined set of ancillary variables in order to properly separate the many causes and modifying factors that combine to ultimately set arterial P_{O_2}/P_{CO_2}. While this article provides some tools to enable such analysis, the practitioner has to decide in each case whether the greater understanding afforded by these ancillary measurements is justified by clinical need.

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