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 O₂ and CO₂) 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 O₂ and CO₂ 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 O₂ 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 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 ($P_{O_2}$ and $P_{EO_2}$ respectively) quantifies the amount of O$_2$ ($V^eO_2$) 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 ($Q$) and the difference between pulmonary venous ($C_{pvO_2}$) and pulmonary arterial ($C_{v\bar{O}_2}$) 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:

$$V^eO_2 = V^e \times (P_{O_2} - P_{EO_2}) = V^a \times (P_{O_2} - FAO_2)$$ \hspace{1cm} (1)

and

$$V^eO_2 = Q' \times (C_{aO_2} - C_{v\bar{O}_2})$$ \hspace{1cm} (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 ($FAO_2$), 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 $P_{AO_2} = FAO_2 \times k$, 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, $V^eO_2$:

$$V^a \times (P_{O_2} - FAO_2) = Q' \times (C_{aO_2} - C_{v\bar{O}_2})$$ \hspace{1cm} (3)

Rearranging the terms gives:

$$V^a/Q' = 8.63 \times (C_{aO_2} - C_{v\bar{O}_2})/(P_{O_2} - P_{AO_2})$$ \hspace{1cm} (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 $C_{v\bar{O}_2}$; and mmHg for both $P_{O_2}$ 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 arterial blood ($P_{O_2}$ and $C_{v\bar{O}_2}$ 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...
HbO₂ dissociation curve particulars. The relationship between \( P_{A\text{O}_2} \) 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 CO₂. Following through the exact same logic presented for O₂, the equation for CO₂ is:

\[
V' A/Q' = 8.63 \times \frac{(C\bar{c}_{CO_2} - C_{aCO_2})/(P_{ACO_2} - P_{CO_2})}{1 + (1 - R)/R}
\]  

(5)

The terms on the right side for CO₂ are reversed (compared to O₂) only because CO₂ is being eliminated from the blood while O₂ 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 O₂ is taken up while CO₂ is eliminated.

Figure 2 is very revealing: When \( V', A/Q' \) is normal (i.e. about 1), \( P_{A\text{O}_2} \) 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 \( P_{A\text{O}_2} \) and blood O₂ 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, \( P_{A\text{O}_2} \) rises while \( P_{ACO_2} \) falls. Because of the differences in the respective dissociation curves, O₂ concentration rises only little, but \( P_{ACO_2} \) and CO₂ concentration fall considerably. This is a profound conclusion: when low \( V', A/Q' \) ratio regions exist, O₂ is seriously affected, more so than CO₂, but when high \( V', A/Q' \) ratio areas develop, CO₂ is the more affected gas.

The alveolar gas equation

The equation for CO₂ corresponding to that for equation 1 for O₂ is now presented:

\[
V' CO_2 = V' A \times (F_{ACO_2} - F_{ICO_2})
\]  

(6)

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

\[
V' CO_2/V' O_2 = R = F_{ACO_2}/(F_{P_{O_2}} - F_{A_{O_2}}) = P_{ACO_2}/(P_{O_2} - P_{A_{O_2}})
\]  

(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:

\[
P_{A_{O_2}} = P_{O_2} - P_{ACO_2}/R
\]  

(8)

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]:

\[
P_{A_{O_2}} = P_{O_2} - P_{ACO_2}/R + P_{ACO_2} \times P_{O_2} \times (1 - R)/R
\]  

(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 ($V'C_O_2$) and the alveolar-arterial $P_{O_2}$ difference ($P_{A-O_2}$, see below). Arterial $P_{O_2}$ will fall; arterial $P_{CO_2}$ and $P_{A-O_2}$ will rise (solid lines); $V'O_2$ and $V'C_O_2$ 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 $V'C_O_2$ 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 $PA_{O_2}$ and hence also arterial $P_{O_2}$. At the same time, $PACO_2$, and thus arterial $PCO_2$ 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 $P_{CO_2}$.

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 $P_{O_2}$ ($P_{O_2}$) 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 $PAO_2$ will fall exactly as much as $P_{O_2}$ as the latter is reduced, if $P_{CO_2}$ and $R$ stay constant. In reality, $PAO_2$ will not decrease as much as $P_{O_2}$ 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 $PAO_2$ 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.

**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 hyperventilation). Figure 5 shows these effects quantitatively. Normal resting alveolar ventilation is about 5 L·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 O₂, where the increase in P\text{O}_2 is usually more modest. As a result, V\text{A}/Q\text{A} inequality essentially always results in hypoxaemia, although arterial P\text{CO}_2 can be high, normal or low, depending on the amount of compensatory hyperventilation.

A final important point about V\text{A}/Q\text{A} inequality is that while it causes significant hypoxaemia breathing room air, arterial P\text{O}_2 increases to levels seen in normal subjects compared to sea levels values as shown. Reproduced with permission from the publisher [4].

**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 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 O₂, CO and CO₂), 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.

**FIGURE 4**

Alveolar oxygen and carbon dioxide partial pressures (P\text{O}_2 and P\text{CO}_2) measured in normal subjects with acute and chronic altitude exposure. Hypoxia-driven hyperventilation reduces P\text{CO}_2 and raises P\text{O}_2 compared to sea levels values as shown. Reproduced with permission from the publisher [4].

**FIGURE 5**

Alveolar partial pressure of oxygen (P\text{O}_2) (from solving equation 1) and P\text{CO}_2 (from equation 6) as a function of alveolar ventilation in a normal lung. Note how sensitive both P\text{O}_2 and P\text{CO}_2 are to small decreases in ventilation.
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 (DL) to the product of blood flow (Q) and β; that is, to DL/[βQ]. Here, β is the overall "solubility" of the gas in blood. For O2 it is approximated by the ratio of arterial-mixed venous O2 concentration difference to arterial-mixed venous PO2 difference, which indicates the average slope of the O2 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 PO2 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 PO2 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 measurable 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 O2 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 CO2 has not so far been documented. The diffusing capacity of CO2 across the bloodgas barrier (quantity of CO2 transported per minute per mmHg partial pressure difference across that barrier) is much greater than for O2. This is because of the approximately 20-fold greater physical solubility of CO2 in the blood gas barrier. However, the capacity of the blood to hold CO2 (as bicarbonate, dissolved CO2 and carbamino-Hb), per mmHg PCO2, is approximately 10-fold greater than that of blood to hold O2 (per mmHg PO2). This acts to partly counterbalance the higher barrier solubility just mentioned such that the time to equilibration for CO2 is not 20 times less than for O2 but more like only two-fold less. Even considering that the chemical reaction steps whereby CO2 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), CO2 appears to equilibrate faster than does O2.

**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 PO2 is usually not very responsive to increases in PO2 in such patients (in contrast to what is seen with V'/A/Q' inequality, see above). Thus, shunting is best quantified when the patient breathes 100% O2 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 PO2 are dramatic and well-known, shunting can also affect arterial PCO2 (and, as mentioned in the introduction, the exchange of all gases). Arterial PCO2 will increase when shunts develop (unless compensated by hyperventilation as commonly occurs). This is because shunted blood, carrying CO2 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 PCO2 by only a mmHg or two, but the relationship between shunt fraction and arterial PCO2 is quite nonlinear, and when shunt is very high, 40–50% of the cardiac output, arterial PCO2 can rise by more than 10 mmHg (again, in the absence of ventilatory compensation).
Cause 6: reduction in pulmonary arterial $P_{O_2}$ ($P_{A\bar{O}_2}$)

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 $P_{v\bar{O}_2}$ will cause a fall in arterial $P_{O_2}$: the perfectly homogeneous lung. In this case, $P_{A\bar{O}_2}$ is governed by having to fulfil the conditions of equation 1 above, making it dependent only on $V_{O_2}$, $V_{A}$ and $F_{I\bar{O}_2}$ (and thus not on $P_{v\bar{O}_2}$). Because the lung is homogeneous, $P_{aO_2}$ must equal $P_{A\bar{O}_2}$ and is thus also unaffected by changes in $P_{v\bar{O}_2}$. 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 $P_{O_2}$. Its effect is evident from equation 4. Thus, if $P_{v\bar{O}_2}$ falls, so too will $P_{A\bar{O}_2}$, 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 $O_2$ 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 $P_{I\bar{O}_2}$ (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–PCO2 relationships) is beyond the scope of this article and is not addressed.

The minimal requirement is an arterial blood gas sample in which the PO2, PCO2, pH, haemoglobin level and O2 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 PO2, PCO2, 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 PO2 (P[i]O2) for the particular altitude, and then inserting the actual arterial PCO2 of the patient. In the critically ill breathing gas higher than 21% in O2, analysis may include dividing arterial PO2 by inspired O2 concentration (to yield the PaO2/P[i]O2 ratio). This is an attempt to correct for PO2 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 PO2 and PCO2 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 Pa–aO2 difference.

The outcomes of this level of analysis are simply to know whether PO2 is within the normal range (accounting for age, altitude, P[i]O2 and temperature), and similarly if PCO2 is low (<35 mm Hg); normal (35–45 mm Hg); or high (>45 mm Hg). Figures 7 and 8 show how arterial PO2 and the PaO2/P[i]O2 ratio behave over a range of values of PO2 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 a range of PO2 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 PO2 selected [20].

**Level 2: calculate Pa–aO2 from the alveolar gas equation** (i.e. equation 8), using the measured arterial PCO2 (PaCO2) in place of alveolar PCO2 (P[i]CO2), 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 Pa–aO2 as the equation implies. For example, at normal arterial PCO2 (40 mmHg) and R=0.8, PaO2 would be 99 mmHg (room air, sea level). However, if R were 0.7, PaO2 would be 92 mmHg, and if R=1, PaO2 would be 109 mmHg.

Equation 8 yields the alveolar PO2 value, and all that needs to be done is to subtract the measured arterial PO2 to give Pa–aO2. 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 PaCO2 and R in to equations 8 and 9 will show.

Breathing room air, Pa–aO2 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, Pa–aO2 is a noisy variable because it represents the usually small difference between two large numbers (alveolar and arterial PO2). Also, recall that it is based on steady state assumptions, as mentioned earlier, and so in a patient whose condition is rapidly changing, Pa–aO2 will not be reliable.

What Pa–aO2 provides over and above PO2 and PCO2 from level 1 analysis is the power to discriminate amongst some of the causes of hypoxaemia. Thus, if Pa–aO2 is normal yet there is hypoxaemia, one of the first two causes (reduced PO2, hypoventilation, respectively) must be the explanation for the reduced arterial PO2. Distinguishing between the first two causes should be self-evident from knowing PO2 and examining arterial PCO2, 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 $P_{O2}$ 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:

$$\frac{CaO_2 \times Q_T - CiO_2 \times Q_s + CvO_2 \times Q_s}{Q_s} = 0$$

Which from equation (2) can be rewritten as:

$$\frac{Qs/Q_T}{100} = \frac{(CiO_2 - CaO_2)/((CiO_2 - CaO_2) + (CaO_2 - CvO_2))}{Q_T}$$

Another form of this equation is:

$$\frac{Qs/Q_T}{100} = \frac{(CiO_2 - CaO_2)/((CiO_2 - CaO_2) + (CaO_2 - CvO_2))(V'A/Q')}{Q_T}$$

FIGURE 7 a) Arterial partial oxygen pressure ($P_{aO2}$) and b) $P_{aO2}$/inspired oxygen fraction ($F_{IO2}$) ratio as a function of $P_{O2}$ in lungs simulated to have only alveolar ventilation/perfusion ($V'A/Q'$) inequality and no shunt. Note that with moderate to severe inequality, $P_{aO2}/F_{IO2}$ is far from constant as $P_{O2}$ changes.
Where $C_iO_2$, $C_aO_2$ and $C_vO_2$ are all in mL·dL$^{-1}$, $V\cdot O_2$ is in mL·min$^{-1}$ and $Q\cdot T$ 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:

$$C_iO_2 = 1.39 \times [Hb] \times \text{fractional O}_2 \text{ saturation (calculated for the value of P}_{\text{A}O_2}) + 0.003 \times P_{\text{A}O_2}$$

$$C_aO_2 = 1.39 \times [Hb] \times \text{fractional O}_2 \text{ saturation (measured in arterial blood)} + 0.003 \times P_{\text{A}O_2}$$

Whether you choose to use equation 11 or equation 12 depends on whether you know $C_vO_2$ or alternatively $V\cdot O_2$ and $Q\cdot T$. 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 $F\cdot IO_2$, 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 $V\cdot O_2/Q\cdot T$ relationship if present. It is not possible to separate these potential contributors just from looking at $Q_S/Q_T$ itself, but the number obtained is a good overall index of the total gas exchange defect at the $F\cdot IO_2$ experienced by the patient. Its utility beyond that of $P_{A\cdot a}O_2$ 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 $V\cdot A/Q\cdot T$ 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 \( (V^E, \text{equation 1}) \) 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:

\[
V^E \times P_{ECO_2} = (V^E - V^D) \times P_{aCO_2} + V^D \times \text{zero} \tag{13}
\]

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:

\[
V^D/V^E = 100 \times (P_{aCO_2} - P_{ECO_2})/P_{aCO_2} \tag{14}
\]

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 (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 $\text{kg}^{-1}$ in subjects with normal BMI is reasonable [25]. In very obese subjects, one should probably use 2 mL $\text{kg}^{-1}$ 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 $V_T$ 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 $Q_s/Q_T$, and the concept is very similar. The only real difference is that in level 3, ambient $F_{O_2}$ 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

![Figure 10](image-url)
hypoxaemia contributing to Qs/Qt. 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 PO₂ is very small. Usually, the resulting value of Qs/Qt on 100% O₂ is less than that measured at lower PO₂, because contributions from V′A/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 PO₂ to be lower than it really was in the sample when collected. Small air bubbles in the sampling syringe, continuing metabolic use of O₂ by white cells in the sample, air contamination during measurement and O₂ consumption by the blood gas electrodes themselves during measurement all pull the PO₂ 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% O₂ affects indices of arterial oxygenation.

Level 5: assessment of extrapulmonary modifying factors: V′O₂, cardiac output (Q′T), Hb concentration, temperature, Hb P50, pulmonary arterial PH. 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 V′O₂ (mL·min⁻¹) to Q′T (L·min⁻¹) exceeds 50, the value of PO₂ 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 PO₂ on arterial PO₂ is when the lungs have no V′A/Q′ inequality or diffusion limitation at all. In this case, all alveoli have the same PO₂ (alveolar and end-capillary) that is determined, as can be seen by examining equation 1, only by metabolic rate (V′O₂), alveolar ventilation (V′A) and inspired O₂ fraction (P(O₂)). The effect becomes greater with increasing amounts of V′A/Q′ inequality. In health, the amount of inequality is sufficiently small that a low PO₂ hardly affects arterial PO₂.

Figure 6 exemplifies the degree to which this may affect arterial PO₂ and the shunt calculation. The effects may be considerable. Also, if Hb concentration is very low, PO₂ will be lower than usual. Contributions from alterations in P50 and temperature are generally clinically small and moreover difficult to estimate.

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

<table>
<thead>
<tr>
<th>Cause of hypoxaemia</th>
<th>Typical example</th>
<th>Arterial PO₂</th>
<th>PA–aO₂ difference</th>
<th>Arterial PO₂ on 100% O₂ and Qs/Qt</th>
<th>V′O₂/Q′ ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low inspired PO₂</td>
<td>Altitude</td>
<td>↓</td>
<td>Normal</td>
<td>Normal (for altitude)</td>
<td>Normal or ↓</td>
</tr>
<tr>
<td>Hypoventilation</td>
<td>Narcotic overdose</td>
<td>↑</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>V′A/Q′ inequality</td>
<td>Most lung diseases</td>
<td>↑ or normal or ↓</td>
<td>↑</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Diffusion limitation</td>
<td>Exercise at altitude; interstitial fibrosis</td>
<td>Normal</td>
<td>↑</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Shunts</td>
<td>Acute lung injury</td>
<td>↑ or normal or ↓</td>
<td>↑</td>
<td>PO₂ below normal; Qs/Qt increased</td>
<td>↑ or normal or ↓</td>
</tr>
<tr>
<td>Extrapulmonary: high V′O₂/Q′ ratio (with lung disease)</td>
<td>Heart failure with pulmonary oedema or lung disease</td>
<td>↑ or normal or ↓</td>
<td>↑</td>
<td>Normal (if no shunt)</td>
<td>↑</td>
</tr>
</tbody>
</table>

Cautionary notes: Highly dependent on individual ventilatory responsiveness. Accuracy requires R [V′CO₂/V′O₂] to be known. Potentially large errors if PO₂ is unknown; risk of measurement error in arterial PO₂. Requires V′O₂ and Q′ to be measured.

PO₂: carbon dioxide partial pressure; PO₂: oxygen partial pressure; PA–aO₂: alveolar–arterial PO₂ difference; Qs/Qt: shunt; V′O₂: oxygen uptake; Q′: perfusion; V′A: alveolar ventilation; V′CO₂: carbon dioxide elimination; PO₂: pulmonary arterial PO₂.
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.

References