CHAPTER 6

Pulmonary gas exchange

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In this "overview", pulmonary gas exchange is considered in three sections. The first section (Normal values, Causes of hypoxaemia I, Respiratory failure) contains "basic" knowledge about pulmonary gas exchange, which is relevant to all who work in clinical medicine. Normal values for arterial oxygen partial pressure, content and Hb saturation ($P_{a,O2}$, $C_{a,O2}$, $S_{a,O2}$) are reviewed, and ventilation–perfusion mismatch and alveolar hypoventilation are highlighted as the two commonest causes of a low $P_{a,O2}$ and respiratory failure. Different types of respiratory failure are discussed, with special emphasis on the hypoxaemia and hypercapnia occurring in chronic obstructive pulmonary disease (COPD) patients in failure (alveolar ventilation–perfusion ($V'\bar{A}/Q'$) mismatch effect) and the rise in arterial carbon dioxide partial pressure ($P_{a,CO2}$) with uncontrolled O2 therapy (alveolar hypoventilation effect).

The next section (Oxygen carriage in blood, Heterogeneity of ventilation and perfusion, Causes of hypoxaemia II) focuses on "intermediate" knowledge, with which all respiratory specialists should be familiar. First, the relationship between oxygen content ($CO_2$) (and oxygen Hb saturation ($SO_2$)) and oxygen partial pressure ($PO_2$), the so-called oxygen dissociation curve (ODC), is introduced. The $P_{50}$ (partial pressure at half maximum blood concentration) for oxygen is defined. Heterogeneity of $V'\bar{A}$ and $Q'$ (leading to $V'\bar{A}/Q'$ mismatch) is analysed using the $PO_2$–$PCO_2$ diagram, the Riley three compartment model (physiological shunt flow/total pulmonary blood flow [$Q'/Q'T$] and dead space (dead space/tidal volume [$VD/VT$]), and the ideal alveolar–arterial $PO_2$ gradient. The causes of hypoxaemia are outlined, and a possible overlap between intrapulmonary shunt and diffusion limitation is discussed using the hepatopulmonary syndrome as an example. The theoretical basis of transcutaneous measurements of $P_{a,O2}$ and $P_{a,CO2}$ (high skin blood flow and a narrow arteriovenous partial pressure difference) and $S_{a,O2}$ is mentioned.

The last section (Oxygen affinity in special situations, Diffusion, Inert gas transport) contains "advanced" knowledge, appropriate for staff in intensive care units, anaesthesiology or rehabilitation, or those undertaking research. The $P_{50}$ for oxygen is reviewed in special situations (right shift in exercise and some haemoglobinopathies, left shift in CO poisoning, in utero and on the Mt Everest summit). The importance of gas phase diffusion within the acinus is emphasised. The pathogenesis of alveolar–capillary diffusion and diffusion limitation for oxygen on exercise (in lung fibrosis and at extreme altitude) is explained. Lastly, inert gas transport is reviewed, focusing on the multiple inert gas elimination technique (MIGET), a sophisticated analysis of $V'\bar{A}/Q'$ mismatch, which has provided information on the pathogenesis of hypoxaemia in different clinical situations.

Normal values

Arterial oxygen tension

$P_{a,O2}$ in normal subjects is affected by several factors: age, body mass index (BMI), posture, altitude and inspired oxygen fraction ($F_{I,O2}$; normal=0.21 or 21%).

The units of $P_{a,O2}$, $P_{a,CO2}$ are kilopascals (kPa) in Europe, but mmHg in North America (1 kPa=7.5 mmHg).

$$P_{a,O2}(\text{kPa}) = 19.15 - (0.052 \times \text{age}) - (0.075 \times \text{BMI}) - (0.076 \times P_{a,CO2}) \ [\text{SEE 1.0}] \ (1)$$

These values [1] were established in lifelong nonsmoking subjects with normal pulmonary function. $P_{a,O2}$ on average declines by 0.55 kPa per 10 yrs from 13.3 kPa at age 20 yrs to 10.7 kPa at age 70 yrs. $P_{a,O2}$ rises by about 1.3 kPa in pregnancy (with a corresponding fall in $P_{a,CO2}$) [2], but there are no other sex effects. The fall in $P_{a,O2}$ with age is caused by an increase in $V'\alpha/Q'$ mismatching. In obese middle aged and elderly subjects, $P_{a,O2}$ is lower in the supine position [3] due to dependent zone bronchiolar collapse (and possibly atelectasis). People living or climbing at altitude, or flying in pressurised aircraft at 9,850–10,770 m have a reduced partial pressure of inspired oxygen ($F_{I,O2}$) and, as a result, a low $P_{a,O2}$ [4]. They may compensate, to some extent, by hyperventilating, which lowers $P_{a,CO2}$ and raises $P_{a,O2}$ (by a roughly equivalent amount). The $F_{I,O2}$ of air (~21%) is unchanged at altitude, but total barometric pressure and the partial pressures of O2 and N2 fall.

Clinically, $F_{I,O2}$ is often increased as a therapeutic measure; if 100% O2 is breathed at sea level, $P_{a,O2}$ in normal subjects may rise from 13.3 to 80 kPa. It is important to know the inspired concentration of oxygen when interpreting a $P_{a,O2}$ value.

The $P_{a,CO2}$ is not affected by age, but it is lowered by hyperventilation, the usual causes being hypoxaemia, metabolic acidosis (e.g. diabetic) and anxiety.

Arterial oxygen content and saturation

Breathing air, 98.5% of oxygen in arterial blood is bound to haemoglobin. At a "normal" Hb concentration (say 14.8 g·dL$^{-1}$) each litre of arterial blood carries 200 mL of oxygen, but only 100 mL·L$^{-1}$ if [Hb] is 7.4 g·dL$^{-1}$. At rest, the arteriovenous (a–v) oxygen content difference is 50 mL·L$^{-1}$ so that mixed venous blood (assuming a normal cardiac output) contains 150 mL·L$^{-1}$ (75% of the arterial value), but only 50 mL·L$^{-1}$ (25% of the normal arterial content) at [Hb] 7.4 g·dL$^{-1}$.

$C_{a,O2}$ is not measured routinely. It can be calculated (in mL·L$^{-1}$) by plotting $P_{a,O2}$ on a standard oxygen dissociation curve (ODC) (see section Oxygen carriage in blood and fig. 1) reading off the percentage saturation of Hb (HbO2) with oxygen at that $P_{a,O2}$ and then multiplying by the [Hb] and the O2 capacity of blood (1.39 g·dL$^{-1}$). Nevertheless, it is now very easy to measure HbO2 % saturation with a pulse oximeter attached to a finger or an ear lobe. Pulse oximetry detects light transmitted at two wavelengths, corresponding to deoxygenated and oxygenated haemoglobin. The signal is the difference in absorbance between the peripheral systolic pulse wave and the subsequent diastole, a difference of only 1–10% of the total light absorbance. Carboxyhaemoglobin (HbCO) (and methaemoglobin) absorb light at the same wavelength as deoxyhaemoglobin, so that HbO2 % is overestimated in the presence of HbCO.

The requirements and reservations of pulse oximetry ($S_{p,O2}$) are shown in table 1. With these reservations, pulse oximetry is acceptably accurate at rest and on exercise when compared with simultaneous estimates of $S_{a,O2}$ from arterial blood samples (<2% difference between estimates) [5]. The weakness of pulse oximetry is that it is insensitive
to minor degrees of hypoxaemia; in the $P_aO_2$ range 13.3 down to 10 kPa HbO$_2$ changes only 3% (97.5 to 94.5%) because of the shape of the ODC (see fig. 1). The strength of pulse oximetry is its ability to follow changes – from rest to exercise, from air to oxygen breathing, and for continuous overnight monitoring. The laboratory and domiciliary uses of pulse oximetry are shown below:

- Home oxygen therapy assessment
- Monitoring during exercise tests
- Overnight monitoring for obstructive sleep apnoea (OSA) diagnosis
- Monitoring at home (done by the patient) by day or at night
- Assessment of "fitness to fly" using 15% inspired oxygen
- Substitute for arterial sampling in children or for serial observations

**Causes of hypoxaemia (low arterial oxygen partial pressure)** I

*Ventilation–perfusion mismatching*

In the case of intrapulmonary disease, $V'\dot{A}/Q'$ mismatching is nearly always the cause of arterial hypoxaemia. To understand this, consider the case of suddenly (and simultaneously) blocking the left main pulmonary artery (with an embolus) and the right main bronchus (with a tumour that has bled). Without ventilation, the blood flow (equal to the whole cardiac output) through the right lung would be unoxygenated (once the small oxygen stores in the lung had been exhausted); the $V'\dot{A}/Q'$ ratio would be zero and
the $P_{a,O2}$ and $P_{a,CO2}$ of the blood leaving the right lung would have the same composition as the mixed venous blood entering it. The other lung with ventilation but no blood flow would act as a dead space with a $V'A/Q'$ ratio of infinity and an alveolar $P_{O2}$ and $P_{CO2}$ equal to that in inspired air. A mixture of $V'A/Q'$ ratios of zero and infinity means no effective gas exchange. As $V'A/Q'$ ratios increase from zero and decrease from infinity, gas exchange efficiency increases until the optimum ratio (~0.86) is reached. In real life, there is a spread of $V'A/Q'$ values throughout the lung on either side of this "optimum" value. The larger the spread, the greater the inefficiency of gas exchange. Low $V'A/Q'$ units lead to arterial hypoxaemia (and hypercapnia). High $V'A/Q'$ units contribute wasted ventilation or "dead space". For further information, consult the $P_{O2}$–$P_{CO2}$ diagram discussed in the section Heterogeneity of ventilation and perfusion (see below).

The effect of $V'A/Q'$ mismatch raises $P_{a,CO2}$ as well as lowering $P_{a,O2}$, but the effect on $P_{a,O2}$ is greater. In simple terms, this is because the "a–v" difference for $P_{O2}$ (13.3–5.3= 8 kPa) is much greater than the "v–a" $P_{CO2}$ difference (0.8 kPa). The body's compensation for hypoxaemia and hypercapnia is to increase minute ventilation (hyperventilation). If, for example, $V'A/Q'$ mismatch has caused $P_{a,O2}$ to fall to 8 kPa [$\Delta5.33$ kPa from "normal"] and $P_{a,CO2}$ to rise to 6.8 kPa [$\Delta1.5$ kPa], hyperventilation sufficient to cause a 2 kPa improvement in both blood gas values will result in $P_{a,O2}$ 10 kPa (still abnormal) and $P_{a,CO2}$ 4.8 kPa (slightly low). With $V'A/Q'$ mismatch, $P_{a,O2}$ is nearly always reduced, but $P_{a,CO2}$ may be raised, normal or low depending on the ventilatory response. In the "emphysematous" type of COPD, or "pink puffer", $P_{a,O2}$ may be surprisingly well preserved (e.g. >11 kPa) but at the expense of hyperventilation and a low $P_{a,CO2}$.

**Alveolar hypoventilation**

An inadequate level of ventilation is the other main cause (in ~5% of cases) of hypoxaemia; its origin is usually extrapulmonary and the $P_{a,CO2}$ is always raised. It is caused by insufficient alveolar ventilation [$V'A$] (total ($V'e$) minus anatomic dead space ($V'd$) ventilation) in relation to metabolic demands of oxygen consumption ($V'O2$) and carbon dioxide production ($V'CO2$). Respiratory centre depression (from anaesthetic, sedative or analgesic drugs) or diseases affecting the diaphragm or its nerve supply, or gross restriction of the chest wall (such as severe kyphoscoliosis) all lead to shallow breathing, low $V'e$ and inadequate $V'A$. Shallow breathing, in the long term, may lead to retention of secretions and atelectasis (deep breaths assist in the renewal of the alveolar surfactant lining). Oxygen breathing in exacerbations of COPD may lead to shallower breathing and a further rise in $P_{a,CO2}$ (see section on Respiratory failure). The consequence of alveolar hypoventilation for arterial blood gases is that $P_{a,O2}$ falls and $P_{a,CO2}$ rises in roughly equal amounts. In theory, $\Delta P_{a,CO2}/\Delta P_{a,O2}=0.8$ (where 0.8 is the respiratory quotient (RQ) imposed on the lung by body metabolism), but because of accompanying $V'A/Q'$ mismatch, the fall in $P_{a,O2}$ may equal or exceed the rise in $P_{a,CO2}$. Recognition of hypoventilation must take the clinical context into account rather than relying on the $P_{a,O2}$–$P_{a,CO2}$ pattern, though a rise in $P_{a,CO2}$ is mandatory.

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**Table 1. – The reservations and requirements of pulse oximetry ($S_{p,02}$)**

<table>
<thead>
<tr>
<th>Reservations</th>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate arterial pulsation</td>
<td>Use vasodilator cream</td>
</tr>
<tr>
<td>Carboxy Hb &lt;3%</td>
<td>Avoid smoking for 24 h</td>
</tr>
<tr>
<td>Steady state</td>
<td>Wait for 5 min (minimum)</td>
</tr>
<tr>
<td>Skin pigmentation</td>
<td>Not a problem, but avoid nail polish and very bright lighting</td>
</tr>
</tbody>
</table>

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**GAS EXCHANGE PRINCIPLES**

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Respiratory failure

There is no precise definition of respiratory failure in terms of $P_{a,O2}$ and $P_{a,CO2}$. In clinical terms, acute respiratory failure is an unstable condition when $P_{a,O2}$ and $P_{a,CO2}$ are progressively falling and rising respectively. Chronic respiratory failure is a stable condition associated with: 1) severe hypoxaemia (e.g. $P_{a,O2} < 8$ kPa, $S_{a,O2} < 90\%$) without (Type I) or with (Type II) hypercapnia; or 2) severe hypercapnia ($P_{a,CO2} > 7$ kPa) with mild hypoxaemia ($P_{a,O2} > 10$ kPa) – the latter occurs with extrapulmonary conditions associated with hypoventilation. The actual $P_{a,O2}$ and $P_{a,CO2}$ values defining "failure" are somewhat arbitrary. The common causes of respiratory failure are shown in table 2.

The pathophysiology of different types of acute or acute-on-chronic respiratory failure are set out in table 3. In acute pulmonary gas exchange failure (ARDS), with severe $V'_{A}/Q'$ mismatch and many gas exchange units flooded with plasma transudate or exudates, corresponding to a $V'_{A}/Q'$ of zero, i.e. "physiological shunt", severe hypoxaemia is the problem ($P_{a,O2} < 5$ kPa) and a high $F_{I,O2} (>60\%)$ may be required to achieve a "safe" $P_{a,O2}$ level (>8 kPa). Central CO$_2$ sensitivity remains normal, so hypercapnia does not occur, if hyperventilation can be sustained. Nevertheless, such severe hypoxaemia cannot be tolerated for long, and intermittent positive pressure ventilation (IPPV) with positive end-expiratory pressure will be required. In extrapulmonary failure – whether originating in the brain stem, phrenic nerves or the diaphragm itself – the weak link is not pulmonary gas exchange, but the ability of brain, nerves or muscle to respond to the hypercapnic stimulus. Since gas exchange is nearly normal, $F_{I,O2}$ needs to be increased only slightly, if at all. Ventilatory assistance with nasal intermittent positive pressure (NIPPV), particularly at night, is the cornerstone of treatment.

Chronic obstructive pulmonary disease and respiratory failure

Some patients with stable COPD (those with a less intense ventilatory response to CO$_2$) have a high $P_{a,CO2}$. Compared with normocapnic COPD patients, hypercapnic subjects have low $P_{a,O2}$, higher [Hb] (secondary polycythaemia) and lower resting $V'E$ (table 4), with shallower and more rapid breathing [6]. They are often oedematous, and

Table 2. – The common causes of respiratory failure

<table>
<thead>
<tr>
<th>Primary lung failure</th>
<th>Adult respiratory distress syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuromuscular</td>
<td>Anterior horn cell disease (e.g. poliomyelitis), phrenic nerve paresis, diaphragm myopathy</td>
</tr>
<tr>
<td>CNS failure</td>
<td>Brain stem (respiratory centre) depression or pathology</td>
</tr>
<tr>
<td>Multifactorial</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
</tbody>
</table>

Table 3. – Different types of respiratory failure

<table>
<thead>
<tr>
<th>Cause</th>
<th>$P_{a,CO2}$</th>
<th>$CO_2$ sensitivity</th>
<th>$F_{I,O2}$ need %</th>
<th>NIPPV response</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDS</td>
<td>Variable</td>
<td>Normal</td>
<td>&gt;60%</td>
<td>[IPPV + PEEP]</td>
</tr>
<tr>
<td>Neuromuscular</td>
<td>↑</td>
<td>↓</td>
<td>21–24%</td>
<td>+</td>
</tr>
<tr>
<td>Brain stem</td>
<td>↑</td>
<td>↓</td>
<td>21–24%</td>
<td>+</td>
</tr>
<tr>
<td>COPD exacerbation</td>
<td>↑</td>
<td>↓</td>
<td>24–35%</td>
<td>+</td>
</tr>
</tbody>
</table>

ARDS: adult respiratory distress syndrome; COPD: chronic obstructive pulmonary disease; $P_{a,CO2}$: arterial carbon dioxide partial pressure; $F_{I,O2}$: inspired oxygen fraction; NIPPV: nasal intermittent positive pressure ventilation; IPPV: intermittent positive pressure ventilation; PEEP: positive end-expiratory pressure.

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have been referred to as "blue bloaters". The hypercapnia of COPD patients is attributed to alveolar hypoventilation. In this case, the hypoventilation is "functional" rather than "actual", meaning that a large proportion of the $V_T$ is ineffective, going to units with a high $V'\frac{A}{Q}$ ratio, and acting as alveolar dead space. COPD is associated with severe $V'\frac{A}{Q}$ mismatch [7], with about one third of pulmonary blood flow going to alveolar units with very low alveolar ventilation and contributing little to CO$_2$ excretion (wasted perfusion); thus, ~33% of pulmonary blood flow receives 10% of total alveolar ventilation, and the resulting low $V'\frac{A}{Q}$ and its uneven distribution is responsible for the hypoxaemia and hypercapnia. In fact, total $V'_E$ is normal (table 4).

In an exacerbation of COPD, $P_{a,CO_2}$ rises and hypercapnia worsens, especially if uncontrolled inspired oxygen ($F_{I,O_2}>28\%$) is prescribed [8]. The rise in $P_{a,CO_2}$ due to the respiratory infection alone is caused by increasing $V'\frac{A}{Q}$ mismatch (bronchiolar

<table>
<thead>
<tr>
<th>$P_{a,O_2}$: arterial oxygen partial pressure; $P_{a,CO_2}$: arterial carbon dioxide partial pressure; $V'_E$: minute ventilation; $f$: respiratory frequency; $V_T$: tidal volume; *: $V'_E$ would be 40% lower if measurements were to be made without a mouthpiece and noseclip. Adapted from GORINI et al. [6].</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>$P_{a,O_2}$ kPa/mmHg</td>
</tr>
<tr>
<td>$P_{a,CO_2}$ kPa/mmHg</td>
</tr>
<tr>
<td>$V'_E$ L/min$^{-1}$</td>
</tr>
<tr>
<td>$f$ min$^{-1}$</td>
</tr>
<tr>
<td>$V_T$ L</td>
</tr>
</tbody>
</table>

Fig. 2. – Hyperbolic relationship between arterial carbon dioxide partial pressure ($P_{a,CO_2}$) and "effective" alveolar ventilation ($\sim [V_T (1 - V_D/V_T) \times f]$) at constant CO$_2$ production ($V'_CO_2$) with data from AUHIER et al. [8] at constant CO$_2$ production ($V'_CO_2$) with data from AUHIER et al. [8] imposed. As $P_{a,CO_2}$ rises in acute (B) on chronic (A) respiratory failure, so its sensitivity to a fall in alveolar ventilation increases, and small falls in tidal volume produced by removal of hypoxic ventilatory drive (see (C)) exacerbate hypercapnia. $V'\frac{A}{Q}$: alveolar ventilation–perfusion; $V_T$: tidal volume; $V_D$: dead space. See table 5 for details.
inflammation and obstruction, alveolar consolidation and collapse) and a decrease in "effective" alveolar ventilation (fig. 2, A→B). STRADLING [9] has shown that the subsequent rise in $P_{a,CO}$ with uncontrolled O$_2$ therapy is due to removal of the hypoxaemic stimulus to central respiratory drive, leading to "true" alveolar hypoventilation (fig. 2, B→C). Figure 2 shows that, at a constant CO$_2$ output, the relationship between alveolar ventilation (for uniformly perfused and ventilated units) and $P_{a,CO}$ is hyperbolic, so that if $P_{a,CO}$ is already raised (fig. 2, point B), a small fall in $V'/A$ ($0.65$ L/min$^{-1}$, in this example), caused by a fall in $V_t$ from 341 to 323 mL is sufficient to raise $P_{a,CO}$ significantly.

Oxygen carriage in blood

The ODC (fig. 1) plays an important role in gas exchange, especially in oxygen delivery to the tissues. At a normal [Hb], >98% of O$_2$ is Hb-bound; thus, it is convenient to substitute for the oxygen content of arterial blood the per cent binding (saturation, $S$) of Hb with O$_2$, the $S_{a,O_2}$. This presupposes that [Hb] is normal. A severely anaemic patient may be very breathless on exercise in spite of a normal $P_{a,O_2}$ and $S_{a,O_2}$! In a normal lung, the fraction of arterial oxygen carried in plasma rises from 2.5% at $P_{a,O_2}$ 13.3 kPa to 8% when plasma $P_{a,O_2}$ is raised to 80 kPa with 100% oxygen breathing; this reservoir of O$_2$ (33% of requirements at rest) is a useful resource when Hb is compromised, as in carbon monoxide (CO) poisoning.

The $P_{O_2}$ at half maximum blood oxygen concentration ($P_{50}$)

The $P_{50}$ defines the position of the ODC with respect to the $P_{O_2}$ axis. The normal value for $P_{50}$ is 3.5–3.7 kPa. A shift to the right (see fig. 1) unloads oxygen to the tissues in the sense of a lower oxygen content for the same $P_{O_2}$; this is advantageous during strenuous exercise, and the right shift is facilitated (see fig. 1) by exercise-related increases in tissue $P_{CO_2}$, hydrogen ion and temperature. 2,3-diphosphoglycerate (2,3-DPG) is a metabolic intermediate in the glycolytic pathway; its concentration in red cells increases in anaemia and hypoxaemia and promotes unloading of O$_2$ to the tissues. The shift to the left promotes oxygen loading from lung to blood (higher oxygen content for the same $P_{O_2}$), and is generally considered disadvantageous; but in circumstances where arterial hypoxaemia is very severe (and associated with polycythaemia), such as in the foetus and at extreme altitudes, the overall effect on tissue oxygen delivery is beneficial (see later).

Heterogeneity of ventilation and perfusion

Under nearly all circumstances (but see section Alveolar–capillary diffusion below), alveolar $P_{O_2}$ and $P_{CO_2}$ are determined by the ratio of alveolar ventilation to perfusion ($V'/A/Q'$); this ratio, even in normal lungs, varies considerably from one gas exchange unit to the next. The analysis and quantification of this heterogeneity (~gas exchange inefficiency) is based on the $P_{O_2}$–$P_{CO_2}$ diagram (fig. 3) [10, 11]. The conceptual brilliance of this diagram is that: 1) the $V'/A/Q'$ line encompasses all possible $V'/A/Q'$ values throughout the lung (given the $P_{O_2}$ and $P_{CO_2}$ composition of mixed venous blood and the inspired gas); 2) the blood R and gas R lines define every possible value of $P_{O_2}$ and $P_{CO_2}$ in arterial blood and mixed alveolar and expired gas; and 3) the "ideal" point defines a "gold standard" or "perfect" lung, i.e. that value of $P_{O_2}$ and $P_{CO_2}$ the lung would have had
in the absence of $V'/Q'$ heterogeneity. Another key concept is that, in the steady state, blood and gas take up oxygen and excrete carbon dioxide in a ratio called the respiratory exchange ratio (R), \( R = \frac{V_{CO2}}{V_{O2}} \), which is determined for the lung by body metabolism, where it is called the respiratory quotient (RQ); fundamental to this idea is that metabolism of the lung itself makes a negligible contribution to the overall gas R. Thus, the mixed blood and the mixed gas are constrained to lines which, in relation to mixed venous blood and inspired gas, have a fixed exchange ratio (R) \( R = 0.8 \) at rest. The blood R and gas R lines can only meet at a point (the "ideal alveolar" (A) point) where all $V' A/Q'$ ratios have the same value (no heterogeneity); under resting conditions this value is ~0.86.

The composition of arterial blood is "weighted" by contributions from low $V'/Q'$ units (by definition, high $V'/Q'$ units have little blood flow), and mixed alveolar (\( A' \)) and mixed expired (\( E' \)) points are similarly weighted by high $V'/Q'$ units. Thus, increasing $V'/Q'$ heterogeneity drives arterial pressure \( (P_a) \) and alveolar pressure \( (P_A) \) (and mixed expiratory pressure \( (P_E) \)) values in different directions down the blood and gas R lines, and the A–a \( P_O2 \) difference becomes an index of gas exchange inefficiency. It is not possible to sample mixed alveolar gas (\( A' \)) because there is always contamination from the anatomic dead space gas, so the ideal point (A) is used as the yardstick. This means that the A–a \( P_O2 \) difference is weighted towards the inefficiency caused by low $V'/Q'$ units.

**The three compartment model of pulmonary gas exchange**

This model (fig. 4) is an extension of the \( P_O2-P_{CO2} \) diagram, using the concept of the "ideal" point in relation to the arterial and mixed expired compositions. It is an "as if"
situation. The lung behaves as if a part was "perfect" (uniformly ventilated and perfused), defined by the "ideal" point, as if another part was perfused but not ventilated at all (called the "physiological shunt"), and as if a third part was ventilated but not perfused (called the "physiological dead space"). For convenience, the "ideal" point is defined in terms of the arterial \( P_{\text{a,CO}_2} \) (in figure 3, the slope of the blood R line between \( P_{\text{a}} \) and the "ideal" point is fairly flat so that \( P_{\text{a,CO}_2} \) lies close to "ideal" \( P_{\text{A,CO}_2} \)) and an assumed value for \( R \) of 0.8. In a simplified form for everyday use:

\[
A - a P_{\text{O}_2} = \left[ P_{1,\text{O}_2} - P_{\text{a,CO}_2}/R \right] - P_{\text{a,O}_2}
\]

(2)

Where the first term (in brackets) is the "ideal" alveolar \( P_{\text{O}_2} \).

Once the "ideal" point has been defined, the physiological shunt ("wasted" blood flow) (conceptually, the distance \( P_{\text{A}} - P_{\text{a}} \) in relation to \( P_{\text{A}} - P_C \)) can be calculated (but in terms of \( O_2 \) contents (\( C \)) not partial pressures) as:

\[
Q' S/ Q' T \% = [C_A - C_a]O_2/([C_A - C_V]O_2 \times 100
\]

(3)

Where \( Q' \)’s is the physiological shunt flow and \( Q' T \) the total pulmonary blood flow.

Dead space ("wasted" ventilation) is traditionally defined in terms of CO\(_2\) exchange, but the principles are similar to the shunt equation; as \( C \) and \( P \) are linearly related in the gas phase, \( P \) is retained:

\[
V_D/V_T = [P_{\text{a,CO}_2} - P_{\text{E,CO}_2}]/P_{\text{a,CO}_2}
\]

(4)

Where \( V_D/V_T \) is the physiological dead space as a proportion of the tidal volume.
*P*$_{a,CO_2}$ is assumed to equal the "ideal" $P_{A,CO_2}$ and $P_{I,CO_2}$ has been omitted from the denominator.

Shunt and dead space are called "physiological" rather than "alveolar", because they both contain an "obligatory" anatomical component, bronchial venous and Thebesian blood flow in the case of shunt and the anatomic dead space in the case of $V_D/V_T$.

### Quantitating gas exchange inefficiency for oxygen

In an earlier section, the $P_{a,O_2}$ was interpreted solely in terms of the normal value for age, BMI and posture. In equations 2, 3 and 4 (see above), gas exchange efficiency is assessed in relation to the "ideal" or perfect lung.

The A–a $P_O_2$ gradient can be calculated from the $P_{a,O_2}$ and $P_{a,CO_2}$, assuming (at rest) R=0.8. Normal values are a function of the inspired $P_O_2$ when $F_{I,O_2}$ $\geq$ 21%; for convenience, the estimates are usually made during air breathing. The normal A–a $P_O_2$ (air) increases with age from 0.8–1.3 kPa at age 20 yrs to 3.5–4.0 kPa at age 70 yrs [12].

For the same amount of physiological shunt ($Q'/s'/Q'$) and $F_{I,O_2}$, the A–a $P_O_2$ declines as $P_{a,CO_2}$ rises (and $P_{a,O_2}$ falls). In spite of these limitations, the A–a $P_O_2$ has been used extensively, and for minor fluctuations in $P_{a,CO_2}$ (5.33±1.0 kPa), gives a better assessment of gas exchange efficiency than $P_{a,O_2}$ alone. In the intensive care setting, A–a $P_O_2$ is very sensitive to $F_{I,O_2}$, and may increase seven-fold from 5.4 to 38 kPa, for the same $Q'/s'/Q'$ (20%), just with an increase in $F_{I,O_2}$ from 21 to 60%. An empirical index, the $P_{a,O_2}/F_{I,O_2}$ ratio, reduces these fluctuations, but does not abolish them.

$Q'/s'/Q'$ requires arterial $O_2$ contents (or saturations) to be calculated from $P_{a,O_2}$ and "ideal" $P_{A,O_2}$ values, and an estimate made of mixed venous (pulmonary arterial) $O_2$ content or saturation (unless right heart catheterisation has been performed). In normal subjects at rest, an a–v difference of 50 mL$^{-1}$ (or $\Delta S_{a,O_2}$ 25%) may be assumed, but in patients with pulmonary hypertension or heart failure that assumption may be wrong.

There is probably more support for the use of the *dead space – tidal volume ratio* ($V_D/V_T$); it is independent of $F_{I,O_2}$, and relatively independent of partial pressure of carbon dioxide in mixed venous blood ($P_{v,CO_2}$). The assumption that $P_{a,CO_2}$=$P_{A,CO_2}$ will be in error if there is a substantial $Q'/s'/Q'$ but as the a–v $P_{CO_2}$ difference at rest is <1.0 kPa, the error will not be large. $V_D/V_T$ is biased towards the detection of units with abnormally high $V'/A'/Q'$. $V_D/V_T$ may help in the interpretation of data, as shown in table 5, based on data in figure 2. Normally, $V_D/V_T$ at rest is <0.4. These patients with stable COPD had hypoxaemia ($P_{a,O_2}$ <8 kPa) and hypercapnia, a normal minute ventilation, but a raised $V_D/V_T$ indicating a degree of $V'/A'/Q'$ mismatch. In an exacerbation of disease, leading to worsening respiratory failure, $P_{a,CO_2}$ rose by 2.5 kPa accompanied by a rise in $V_D/V_T$ and a fall in "effective" tidal volume ($V_T$ actually rose). The fall in $V_T$ (effective) [0.11 L] was

### Table 5. – Respiratory failure in chronic obstructive pulmonary disease (COPD) exacerbations; effects of uncontrolled oxygen therapy

<table>
<thead>
<tr>
<th></th>
<th>Resp rate</th>
<th>$V_T$</th>
<th>$V'E'$</th>
<th>$V_D/V_T$</th>
<th>$V_T$ (effective)* L</th>
<th>Alveolar ventilation* L$^{-1}$</th>
<th>$P_{a,CO_2}$ mmHg</th>
<th>$P_{a,CO_2}$ kPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD: stable</td>
<td>20</td>
<td>0.41</td>
<td>8.2</td>
<td>0.5</td>
<td>0.21</td>
<td>4.11</td>
<td>6.1 [46]</td>
<td></td>
</tr>
<tr>
<td>COPD: failure</td>
<td>31</td>
<td>0.34</td>
<td>10.5</td>
<td>0.77</td>
<td>0.94</td>
<td>2.91</td>
<td>8.7 [65]</td>
<td></td>
</tr>
<tr>
<td>COPD: failure + O$_2$</td>
<td>32</td>
<td>0.32</td>
<td>10.3</td>
<td>0.82</td>
<td>0.073</td>
<td>2.36</td>
<td>11.2 [84]</td>
<td></td>
</tr>
</tbody>
</table>

$V_T$: tidal volume; $V'E'$: minute ventilation; $V_D$: dead space; $P_{a,CO_2}$: arterial carbon dioxide partial pressure; *: $V_T$ (effective)$=[V_T, (1 – V_D/V_T)]$; *: alveolar ventilation$=V_T$ (effective)$\times$resp rate. Adapted from Aubier et al. [8] and Stradling et al. [9].
much greater than the fall in $V_t$ (actual) [0.07 L], indicating severely worsening $V_A/Q_A$ mismatch. Finally (table 5, bottom row), with uncontrolled $O_2$ therapy, there was another substantial rise in $P_{a,CO_2}$ but very little change in $V_D/V_T$; $D_V$ (effective) was the same as $D_V$ (actual), indicating that true hypoventilation was the reason for the rise of $P_{a,CO_2}$ on oxygen [6].

Causes of hypoxaemia (low arterial oxygen partial pressure) II

The cause of the hypoxaemia (table 6) is usually obvious from the clinical diagnosis. Hypoventilation and $V_A/Q_A$ mismatch have been discussed already. In $V_A/Q_A$ mismatch, $P_{a,O_2}$ will only exceed 80 kPa with 15 min 100% $O_2$ breathing if all parts of the lung are aerated (as in COPD), with oxygen diffusing to obstructed alveoli through collateral pathways. In ARDS or pulmonary oedema, waterlogged gas exchange units will be unable to take up oxygen. Diffusion limitation, also called "alveolar–capillary block", occurs on exercise at high altitude, and on exercise in patients with interstitial pulmonary fibrosis (cryptogenic fibrosing alveolitis) whose transfer factor of the lung for carbon monoxide ($T_L,CO$; at rest) is $<50\%$ predicted. Intrapulmonary anatomic right to left shunts (intracardiac R–L shunts behave similarly as regards $P_{a,O_2}$) are unusual. The most frequent causes are pulmonary arteriovenous malformations (PAVMs), associated with hereditary haemorrhagic telangiectasia [13], and the hepatopulmonary syndrome (HPS), associated with liver disease and portal hypertension [14]. PAVMs can be demonstrated with high resolution computed tomography scans or pulmonary angiography. The shunt channels in HPS are too small to be demonstrated by these techniques; contrast echobubble or albumin macroaggregate radionuclide ($^{99m}$Tc-MAA) lung scans will show contrast material passing through the lung to reach the left side of the heart, or (in the case of $^{99m}$Tc-MAA) the kidneys or brain.

HPS is an interesting condition physiologically because it has features of diffusion limitation as well as those of a R–L intrapulmonary shunt. Many of the capillaries in the alveolar septa are remodelled (cause unknown) with diameters as large as 100–200 $\mu$M (normal 7–15 $\mu$M). The $T_L,CO$ is very reduced (decreased capillary surface area and increased intracapillary diffusion distances) and $P_{a,O_2}$ is low and has a variable response to breathing 100% oxygen. In HPS, a poor response to 100% $O_2$ ($P_{a,O_2} <<80$ kPa) suggests very widened capillaries that act as an intrapulmonary anatomic R–L shunt. On the other hand, a good response to 100% $O_2$ ($P_{a,O_2} >73.3$ kPa) in some HPS patients suggests smaller channels in which diffusion equilibration can be established when the [$P_{a,O_2} – P_{CO_2}$] gradient is raised. With 100% $O_2$ breathing, and arterial sampling for $P_{O_2}$, the R–L shunt can be quantitated, as $Qs/Qt \%$ using equation (3); this gives a "physiological" estimate. The R–L shunt can also be measured (as $Qs/Qt \%$)

| Table 6. – The causes of arterial hypoxaemia |
| Altitude | Low $P_{i,O_2}$ |
| Hypoventilation | $V'E$ inadequate for $V'O_2$; $P_{a,CO_2}$ always raised |
| Diffusion limitation | $D_O2$ inadequate for $V'O_2$; $P_{a,O_2}$ falls ++ on exercise |
| $V_A/Q_A$ mismatch | $P_{a,O_2} >73.3$ kPa on 100% oxygen |
| Anatomic R–L shunt | $P_{a,O_2} <73.3$ kPa on 100% oxygen |

$P_{i,O_2}$: partial pressure of inspired oxygen; $V'E$: minute ventilation; $V'O_2$: oxygen production; $P_{a,CO_2}$: arterial carbon dioxide partial pressure; $P_{a,O_2}$: arterial oxygen partial pressure; $D_O2$: oxygen diffusing capacity of the lung; $V_A/Q_A$: alveolar ventilation–perfusion ratio; R: right; L: Left.
"anatomically" using a $^{99m}$Tc-MAA lung-kidney scan technique, and in large-channel R–L shunts (as in PAVMs) these physiological and anatomic estimates are in agreement. In HPS, the oxygen shunt ($P_{a,O2}$) and the $^{99m}$Tc-MAA shunt were the same breathing air, but with 100% O$_2$ breathing, the physiological shunt was less than the anatomic $^{99m}$Tc-MAA shunt. This suggests an interesting scenario. Breathing air, the low $P_{a,O2}$ in HPS behaves as an intrapulmonary R–L shunt, but conceptually (from the 100% O$_2$ data) it should be regarded as an extreme example of diffusion limitation [14, 15].

Noninvasive measurements of arterial oxygenation

The convenience of measuring arterial oxygen saturation ($S_{a,O2}$) with a finger or ear lobe probe has been stressed earlier. The advantage of sampling arterial blood is that $P_{a,CO2}$ and pH can also be measured. But, arterial sampling is invasive, particularly when repeat measurements are required in ambulatory patients; in intensive care, arterial cannulas will be inserted.

Arterialised capillary blood

A less invasive method of obtaining $P_{a,O2}$, $P_{a,CO2}$ and pH is to sample arterialised capillary blood, obtained by making a small cut in the periphery of the ear lobe, after previous warming with vasodilator cream. Blood, which must be freely flowing, is collected as anaerobically as possible (with stringent precautions to avoid blood spillage and skin pricks), and analysed immediately. Good technique is crucial. The sample is a mixture of capillary and venular blood. The principle is that vasodilatation increases local blood flow up to 10-fold; from the Fick equation, if local $V'_{O2}$ does not change, the arterio–venous content and $PO_2$ difference will narrow sufficiently so that capillary and venous $PO_2$ approach $P_{a,O2}$. In normoxia, the a–v $PO_2$ gradient is large (8 kPa) and arterialised samples tend to underestimate the true arterial value (by 0.6 kPa). But, in hypoxaemia, on the steep part of the ODC, with a smaller a–v $PO_2$ difference (<4 kPa), there is good convergence of arterialised $PO_2$ and $P_{a,O2}$ at $P_{a,O2}$ levels <9.3 kPa [16]. The results on exercise are similar to those at rest. The overall message is that false negatives (falsely normal $P_{a,O2}$) are less of a problem than false positives, i.e. a misleadingly low $P_{a,O2}$.

Transcutaneous measurements ($P_{tc,O2}$)

A Clark polarographic electrode placed on the skin measures the $PO_2$ in subdermal tissues. The principle is the same as when arterialised capillary blood is sampled. Vasodilatation is achieved by heating the skin to 40–42°C, and this narrows the a–v $PO_2$ difference. The method works best in neonates where the epidermis is very thin. Substantial underestimates may occur in adults, even with gentle abrasion of the epidermis. Calibration against a simultaneous arterial sample is needed. In adults, transcutaneous oxygen tension ($P_{tc,O2}$) may be able to follow trends in $P_{a,O2}$ over time, but spot samples are not reliable.

Measurement of $P_{a,CO2}$ with transcutaneous electrodes is well established as a reliable monitor of long-term trends, i.e. overnight in patients with nocturnal hypoventilation. The small arteriovenous difference for $P_{a,CO2}$ at rest is an advantage.
Oxygen affinity in special situations

**Haemoglobinopathies**

The importance of the position of the ODC, as defined by the $P_{50}$ (normal value 3.5–3.7 kPa), was stressed earlier. Shifts to the right in anaemia and hypoxaemia, produced by an increase in red cell 2,3-DPG, promotes efficient oxygen unloading to tissues (larger arteriovenous oxygen content difference ($\Delta [\text{Ca}–\text{Cv}]\text{O}_2$) for the same arteriovenous $P_{\text{O}2}$ difference ($\Delta [\text{Pa}–\text{Pv}\text{O}_2]$)). In normoxia, shifts to the left (less O2 unloading) are considered disadvantageous. Certain congenital haemoglobinopathies are associated with large right or left $P_{50}$ shifts (table 7). A right shift, such as occurs in Hb Seattle is associated with anaemia (Hb 60% normal); even so, the normal a–v O2 content difference at rest (45–50 mL·L$^{-1}$) can be unloaded at a nearly normal $P_{\text{vO}2}$ (4.7–5.1 kPa); exercise capacity is relatively unimpaired. On the other hand, haemoglobinopathies with a left shift develop polycythaemia to compensate for their difficulty in O2 unloading. Hb Andrew–Minneapolis [17] has [Hb] 117% normal. Because of the increase in the O2 content of arterial blood, such patients can deliver 45–50 mL·L$^{-1}$ to the tissues in the normal range of $P_{\text{vO}2}$ (6.1 kPa).

Apart from haemoglobinopathies, shifts to the left (↓ $P_{50}$) occur in three other situations: 1) CO poisoning; 2) at extreme altitudes, and 3) in the foetus. The $P_{50}$ shift, accompanied by polycythaemia, is beneficial in (2) and (3) but, accompanied by an "effective" anaemia, it is disastrous in (1).

**Carbon monoxide poisoning**

Life is possible with a severe anaemia (Hb 5.8 g·dL$^{-1}$; 40% normal), but replacement of 60% HbO$_2$ with HbCO in acute CO poisoning would be fatal. The very high affinity of CO for Hb (250 times > oxygen), actually caused by its very slow dissociation from Hb, shifts the curve of the residual HbO$_2$/deoxyHb to the left (a competitive antagonism effect) so that $P_{50}$ at HbCO 60% is very low (table 7); at a $P_{\text{vO}2}$ of 2.66 kPa, only 14 mL·L$^{-1}$ of O2 would be unloaded, just 27% of the oxygen requirements at rest. In acute poisoning, the situation is made worse by: 1) absence of a compensatory erythropoiesis; and 2) a normal $P_{\text{aO}2}$, and thus no ventilatory or cardiac stimulus to tissue anoxia from the carotid body. At low levels of HbCO%, syncope is common when mild exercise is taken because the increased oxygen demand cannot be met due to the $P_{50}$ shift and the anaemia effect of replacement of HbO$_2$ with HbCO. In severe cases, tissue

---

**Table 7.** – $P_{50}$ (O$_2$ partial pressure at half maximum O$_2$ concentration), oxygen dissociation curve (ODC) shift and haemoglobin (Hb) concentration for human blood in different situations

<table>
<thead>
<tr>
<th>Situation</th>
<th>$P_{50}$</th>
<th>ODC shift</th>
<th>Pathogenesis</th>
<th>[Hb]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>3.5–3.7</td>
<td>26–28</td>
<td>NIL</td>
<td>100</td>
</tr>
<tr>
<td>Exercise</td>
<td>3.8–4.2</td>
<td>29–32</td>
<td>RIGHT</td>
<td>100</td>
</tr>
<tr>
<td>Hb Seattle</td>
<td>5.2</td>
<td>39</td>
<td>RIGHT</td>
<td>60</td>
</tr>
<tr>
<td>Hb Minneapolis</td>
<td>2.3</td>
<td>17</td>
<td>LEFT</td>
<td>117</td>
</tr>
<tr>
<td>Foetal blood</td>
<td>2.6</td>
<td>19</td>
<td>LEFT</td>
<td>133</td>
</tr>
<tr>
<td>Mt Everest summit</td>
<td>2.6</td>
<td>19</td>
<td>LEFT</td>
<td>130</td>
</tr>
<tr>
<td>CO poisoning</td>
<td>1.33</td>
<td>10</td>
<td>LEFT</td>
<td>40</td>
</tr>
<tr>
<td>HbCO 60%</td>
<td></td>
<td></td>
<td>antagonism; frequently fatal</td>
<td></td>
</tr>
</tbody>
</table>

CO: carbon monoxide; Hb-F: foetal haemoglobin; HbO$_2$: oxyhaemoglobin; HbCO: carboxyhaemoglobin; $^\#$: alkalosis overcomes right shift effect of ↑ 2:3 DPG (hypoxaemia induced); $^\dagger$: foetal umbilical blood as per cent maternal uterine blood.
anoxia causes loss of consciousness and ischaemic damage to the brain and heart. Hyperbaric oxygen is an effective therapy if administered in time. At 3.0 ATM, about 50 mL·L⁻¹ of O₂ is dissolved in plasma, which is sufficient to meet O₂ demand at rest [18]. The rate of dissociation of HbCO can be increased from a half time of 5 h on air to 90 min on O₂ at 1.0 ATM or to 23 min at 3.0 ATM [19]. Time is of the essence, but 100% oxygen administered in an ambulance will treat effectively those with mild CO intoxication.

**Extreme altitude**

Ascending to the summit of Mt Everest (8,848 m) is an increasingly popular challenge. Since the first ascent in 1953 by Hillary and Tensing, about 1,400 people have reached the summit (another 180 have died on the mountain). The ascent is generally done breathing oxygen, but a successful ascent has been made, by Messner and Habeler in 1978, breathing air. Pulmonary gas exchange at these extreme altitudes has been studied both in the field (American Medical Research Expedition to Everest (AMREE) 1981) and in hypobaric chamber simulations (Operation Everest II, 1985); some measurements (P₁O₂, Pao₂, Paco₂, heart rate) have been made standing on the summit itself [20].

The most remarkable feature of gas exchange under these extreme conditions (at the limit of the ability of humans to cope with hypoxia [P₁O₂ on the summit=5.73 kPa] is the ability of the body to defend the arterial oxygen tension (P) and content/saturation (C, S). The PₐO₂ on the summit was 4.7 kPa, SₐO₂ was 71% and CₐO₂ was 182 mL·L⁻¹ (91% of normal at sea level) [21]. The very small [P₁–Pₐ] difference for O₂ was produced by extreme hyperventilation (at least five times normal) at rest, lowering arterial PCO₂ to 1.0 kPa and raising pH to 7.7 (normal 7.4). The respiratory alkalosis shifted the estimated P₅₀ to 2.59 kPa and raised SₐO₂ from 40% (at normal P₅₀) to 71% [22]. Secondary polycythaemia raised CₐO₂ from 142 mL·L⁻¹ (at a normal Hb) to 90% of the normal sea level value. At lower altitudes (6,300 m), resting hyperventilation was less, PₐCO₂ was 2.45 kPa, respiratory alkalosis was mild (pH 7.47) and in vivo P₅₀ was normal at 3.7 kPa (the alkalosis effect being offset by a hypoxia-induced 2,3-DPG increase) [22]. The measurements of gas exchange on exercise will be considered in a later section (section Alveolar–capillary diffusion).

**Gas exchange in the foetus**

The P₅₀ of foetal Hb, and the PₐO₂ in the foetal aorta, are similar to the values on the summit of Everest (see previous paragraph), supporting Joseph Barcroft's 1933 description of the foetal environment as "Mt Everest in utero". Foetal [Hb] is also higher than postnatally. There is no alkalosis (PₐCO₂ 5.7 kPa [43 mmHg]), so the P₅₀ shift is driven entirely by the structure of foetal Hb. For an a–v Pₒ₂ difference of 45 mL·L⁻¹, foetal venous Pₒ₂ is low, ~2.7 kPa [20 mmHg] [23]. Exercise requirements are minimal!

**Diffusion**

**The acinus as the gas exchange unit**

Experimentally, pulmonary arteries >150 μM diameter have to be blocked (with beads) before high V’ₐ/Q’ regions emerge [24]. 150 μM corresponds to the diameter of the artery supplying the acinus, supporting the notion that the acinus is the effective gas exchanging unit. There are 33–50,000 (diameter 0.06 mM) acini in the human lung [25].
The entry bronchiole (terminal bronchiole) branches into three generations of alveolated respiratory bronchioles, four generations of alveolar ducts and one of alveolar sacs. There are 250 alveolar sacs per acinus and 30–40 alveoli per sac (1,750 alveoli per acinus). The distance from the terminal bronchiole to the alveolar sacs averages 8 mM (range 5–13 mM); over this distance the cross-sectional area increases exponentially 64 times, like a trumpet. During normal breathing, the acinus and its components expand and contract, but the convective flow in and out contributes little, if anything, to the mixing of inspired oxygen with the residual O₂ present throughout the acinus at the end of the preceding expiration; the same arguments apply, in reverse, to CO₂. Alveolar ventilation, in the sense of bringing inspired O₂ molecules into contact with the alveolar epithelium, occurs entirely by molecular diffusion, which is proportional to the physical diffusivity of O₂ in air multiplied by the surface area/distance ratio. This ratio, because of the anatomy of the acinus, is so high (200 cm²/0.5 cm) that uniformity of alveolar \( P_O₂ \) has occurred by diffusive mixing throughout the acinus by the end of inspiration [26]. Differences in ventilation that occur because of differences in local compliance and resistance (as a result of convective flow inequalities), cause gas concentration differences between acini, but not within acini. In contrast to the uniformity of acinar ventilation, acinar blood flow may be very uneven in time and space, chiefly due to recruitment and derecruitment of pre-capillary arterioles and alveolar septal vessels, which tend to be either "open" or "shut". This intra-acinar non-uniformity is less evident in the dependent zones and on exercise. Nevertheless, the uniformity of end-inspiratory \( P_{A,O₂} \) as a result of molecular gaseous diffusion implies uniformity of end-capillary \( P_{O₂} \) despite non-uniform blood flow within the acinus [26]. Thus, acinar gas exchange is determined by mean ventilation and mean blood flow, and the resulting mean \( V'/Q' \) ratio. The acinus may not behave as the ultimate gas exchange unit in disease when its architecture has been distorted, individual alveoli flooded or alveolar-capillary membranes thickened.

**Alveolar–capillary diffusion**

Oxygen is transferred from gas to blood, from the alveolar epithelial surface to the Hb molecule in the pulmonary capillary erythrocytes, according to the relationship [27]:

\[
V'O₂ = D_L \left[ P_{A} - P_c \right] O₂
\]

Where \( D_L \) is the oxygen diffusing capacity (\( D_{L,O₂} \)), \( P_c \) is the mean capillary \( P_{O₂} \), and \( \left[ P_{A} - P_c \right] \) is the effective (mean) driving pressure. \( D_{L,O₂} \) is a conductance with units of mmol·min⁻¹·kPa⁻¹. \( V'O₂ \) [lung] must match \( V'O₂ \) [body tissues]. Thus, a low exercise \( D_{L,O₂} \), due to interstitial lung disease (ILD), will limit \( V'O₂,max \) unless the gradient \( \left[ P_{A} - P_c \right] \) can be increased proportionately by increasing \( P_{A,O₂} \) (by hyperventilation) or by lowering \( P_{c,O₂} \) by a decrease of \( P_{c,O₂} \) on exercise. While \( P_{c,O₂} \) is one of the determinants of \( V'O₂,max \), it is the end-capillary \( P_{O₂} \) (\( P_{c,O₂} \)) which, in a uniform lung, influences the \( P_{a,O₂} \). In an ideal lung (or gas exchange unit), there is diffusion equilibrium, i.e. \( P_{c,O₂} = P_{a,O₂} \), before blood has left the alveolar region. The end gradient \( \left[ P_{A} - P_c \right] \) for oxygen, the existence of which implies "diffusion limitation", is a function of the diffusion–perfusion conductance ratio:

\[
\frac{\left[ P_{A} - P_c \right]}{\left[ P_{A} - P_c \right]} = e^{-D_L/Q' \beta}
\]

where \( \beta \) for \( O₂ \) is the oxygen capacitance of blood (~ the slope of the ODC at any given \( P_{O₂} \)). \( \beta \) is high when \( P_{A,O₂} \) and \( P_{c,O₂} \) are low and the ODC slope is high. \( Q' \beta \) is the perfusion conductance whose units are (if \( Q' \) is L·min⁻¹) mmol·min⁻¹·kPa⁻¹ – similar...
For DP assuming (at rest), with ILD on exercise, this would mean an end-gradient. The rate of increase of red cell oxygen partial pressure (P\textsubscript{c.O\textsubscript{2}}) at rest is 0.5 kPa – almost complete equilibration. For DP=1.0, alveolar–capillary equilibration is only 63% complete; for a patient with ILD on exercise, this would mean an end-gradient [PA – P\textsubscript{c}] of 6.3 kPa; assuming PA,O\textsubscript{2}=13.3 kPa, PA,O\textsubscript{2} would be <7.0 kPa, i.e. significant hypoxaemia [28].

Figure 5 plots PA and P\textsubscript{c} for oxygen and the Dl/Q\textsubscript{b} ratio (mean value for the whole lung, ignoring regional inhomogeneity) at rest and on moderately severe exercise for a normal subject and a patient with ILD. A small gradient opens up in the normal subject on exercise (\(\Delta Q\textsubscript{b} / \Delta D_l\)) >\(\Delta D_l\)). In ILD with a low Dl, Dl/Q\textsubscript{b} is low at rest, but not sufficient to cause a significant end-gradient; such hypoxaemia as exists is caused by \(\gamma' / Q'\) inequality. Dl/Q\textsubscript{b} ratio falls sharply on exercise (Dl increase is small compared to Q' increase), causing a large [PA – P\textsubscript{c}'] gradient ("diffusion limitation") and exercise-induced hypoxaemia.

Diffusion limitation can occur occasionally in super-fit normal subjects breathing air, undergoing extreme exertion when \(\Delta Q\textsubscript{b} >\Delta D_l\). It occurs with exception on exercise at altitude when PA,O\textsubscript{2} is <8 kPa, because \(\beta_O2\) remains high (on the steep part of the ODC) throughout the time course of blood capillary transit. Theoretical studies suggest that the increase in left shift in the ODC (\(\downarrow P_{\text{aO2}}\)) at altitude promotes more rapid alveolar–capillary equilibration for any given \(P_h, V''O_2\) and Dl,O\textsubscript{2} [29], presumably by lowering \(\beta_O2\).

Extensive measurements of pulmonary gas exchange were made during chronic hypobaric chamber exposure in fit subjects in Operation Everest II [30]. Diffusion limitation was measured using the MIGET technique (see next section) by comparing the A–a PaO\textsubscript{2} actually measured by arterial sampling with that predicted from the \(V''/Q'\) distribution measured by MIGET; when actual gradient >MIGET gradient, diffusion limitation of gas exchange is inferred. Diffusion limitation was detected at sea level at V'O\textsubscript{2} >3.0 L\textperiodcentered min\(^{-1}\), and at progressively lower V'O\textsubscript{2} as Pb and Pl,O\textsubscript{2} decreased. On the "summit", V'O\textsubscript{2,max} was 1.0 L\textperiodcentered min\(^{-1}\) (27% of sea level value), PA,O\textsubscript{2} fell from 4.1 kPa to
3.7 kPa (rest to exercise), and A–aPo₂ increased from 0.2 kPa to 0.96 kPa due to diffusion limitation [30].

Interestingly, patients with Hb Andrew–Minneapolis with a left shift (P₅₀ 2.3 kPa) had (at sea level) a lower V'O₂,max compared with controls, but a higher V'O₂,max than those at moderate altitude (P₁O₂ 13.3 kPa). The authors, somewhat fancifully, termed them "Human Llamas" [17].

Inert gas transport and the MIGET technique

The multiple inert gas elimination technique (MIGET), pioneered by Wagner et al. [31] measures the distribution of $V'\lambda/Q'$ in an "as if" 50 compartment model of the lung; there are 48 compartments with discrete $V'\lambda/Q'$ values from 0.01 to 10 plus shunt ($V'\lambda/Q'=0$) and dead space ($V'\lambda/Q'=\infty$) compartments. MIGET is a considerable advance on the three compartment model (fig. 4) of Riley and Cournand [10], but it is technologically complex and suitable only for research studies. Six inert (nonreactive with Hb) gases with a wide range of solubilities (λ), (λ is similar to the capacitance coefficient, β, except for the units (ATM⁻¹, not kPa⁻¹ or mmHg⁻¹)) are dissolved and infused intravenously for 30 min, after which mixed venous, arterial and mixed expired blood and gas samples are taken and analysed by gas chromatography for the arterial retention ($P_a/P_v$) and alveolar excretion ($P_A/P_v$) ratio of each gas (fig. 6). The key relationship is:

$$P_a/P_v=\lambda/[\lambda+V'\lambda/Q']$$  \hspace{1cm} (7)

Figure 6 shows that 50% retention ($P_a/P_v=0.5$) occurs with a $V'\lambda/Q'$ ratio <0.1 for
low solubility (λ) gases, but with a $V'_{A}/Q'$ ratio $>10$ for high solubility gases. It follows that SF$_6$, the gas with the lowest solubility, only has a positive $P_{a}/P_v$ value from low $V'_{A}/Q'$ units and shunt, for which it is the marker of choice. Conversely, the highest solubility gas, acetone, is only retained in arterial blood from units with $V'_{A}/Q' >1.0$, so it is a marker of high $V'_{A}/Q'$ units and alveolar dead space. In figure 6b, the overall lung retention of each gas in arterial blood (a) and alveolar gas (A) is plotted in relation to an ideal lung (h) uniformly perfused and ventilated. The shape of the arterial (a) and alveolar (A) lines, and the (a–h) and (h–A) pattern for the array of inert gases (analogous to the A–a $P_{O2}$) is unique for a particular $V'_{A}/Q'$ distribution, which can be analysed and plotted as shown in figure 6c. The left-hand end of the blood flow versus $V'_{A}/Q'$ plot reflects poorly ventilated units, not poorly perfused units, while the right-hand end of the ventilation versus $V'_{A}/Q'$ plot highlights units with poor perfusion. Much information about $V'_{A}/Q'$ distributions in different respiratory conditions has been obtained with the MIGET technique; an excellent review is available [32] and West's little book [33] is an invaluable teaching aid.

Conclusions

$P_{a,O2}$ and $P_{a,CO2}$ are determined by several factors, principally by the properties of: 1) blood; 2) the lung; and 3) systems controlling minute ventilation and cardiac output. The S–shaped oxygen dissociation curve (ODC) (fig. 1) is responsible for much of the complexity of oxygen uptake from lung to blood, its shape determining the form of the $V'_{A}/Q'$ lines and blood R in the $P_{O2}$–$P_{CO2}$ diagram (fig. 3). The $P_{50}$ for oxygen is an important determinant of tissue oxygen delivery (table 7). In an ideal lung, all gas exchange units would have an optimum ratio of ventilation to blood flow ($V'_{A}/Q'$) (~0.86); heterogeneity of the ratio, due to uneven distributions of $V'_{A}$ and $Q'$, causes $V'_{A}/Q'$ mismatch and is the chief cause of arterial hypoxaemia (low $P_{a,O2}$). Respiratory failure may occur as a result of overwhelming intrapulmonary shunt (e.g. ARDS), $V'_{A}/Q'$ mismatch (e.g. COPD) or alveolar hypoventilation (extrapulmonary causes). Diffusion limitation to gas exchange is a cause of arterial hypoxaemia in special circumstances: 1) when $D_{L,CO}$ (~$D_{L,O2}$) is low and cardiac output ($Q'$) is high (patients with lung fibrosis exercising); and 2) in normal subjects exercising at extreme altitude.

Summary

1. The arterial oxygen tension ($P_{a,O2}$) in normal subjects is affected by several factors, principally age, altitude and the inspired oxygen fraction ($F_{I,O2}$). The arterial carbon dioxide tension ($P_{a,CO2}$) is not affected by age, but is lowered by the hyperventilation of pregnancy and by anxiety. In arterial blood 98–99% of oxygen is bound to haemoglobin (Hb). Pulse oximetry is a simple noninvasive way of estimating the oxygen saturation of Hb in arterial blood ($S_{a,O2}$) [normal=97.5%]. In anaemia, with Hb concentration 50% normal, $S_{a,O2}$ and $P_{a,O2}$ will be normal, but arterial oxygen content ($C_{a,O2}$) will be only 50%.

2. The commonest clinical cause (in 90% of cases) of a low $P_{a,O2}$ is uneven distribution of alveolar ventilation ($V_A'$) and perfusion ($Q'$), so-called $V'_{A}/Q'$ mismatch. The cause is intrapulmonary disease affecting the bronchi, alveoli and/ or pulmonary circulation. The second cause (in 8%) is extrapulmonary (e.g. respiratory muscle
weakness, loss of CO₂ chemosensitivity), involving insufficient total ventilation, often with a tidal volume that is too small to clear the obligatory anatomic dead space completely.

3. In chronic respiratory failure, the \( P_{a,O₂} \) and \( S_{a,O₂} \) are severely reduced (\( P_{a,CO₂} \) may be low, normal or high). In acute respiratory failure, often associated with shallow breathing and an extrapulmonary cause, the \( P_{a,CO₂} \) is usually raised as much as the \( P_{a,O₂} \) is lowered. An increase in \( F_{l,O₂} \) restores \( P_{a,O₂} \) to a "normal" level for air breathing, whatever the cause of the respiratory failure. In the acute on chronic respiratory failure of chronic obstructive pulmonary disease (COPD), an \( F_{l,O₂} \) increase may exacerbate the shallow breathing and lead to a further rise in \( P_{a,CO₂} \).

4. The relationship between the oxygen content \( (C_O₂) \) of blood and its partial pressure \( (P_{O₂}) \) – the oxygen dissociation curve (ODC) – is sigmoid in shape. The position of the curve on the \( P_{O₂} \) axis is defined by the \( P_{50} \). A left shift (low \( P_{50} \)) promotes oxygen loading in the lung, and a right shift increases oxygen unloading to the tissues. Both may be advantageous in the right circumstances – the left shift in the foetus, and at extreme altitude (though the left shift in carbon monoxide poisoning may be fatal), and the right shift in strenuous exercise.

5. The normal range for \( P_{a,O₂} \) is quite wide. The "efficiency" of pulmonary gas exchange is often assessed, on a quantitative basis, in terms of a physiological dead space/tidal volume ratio \( (V_D/V_T) \), reflecting abnormally high \( V''A/Q'' \) ratios, physiological shunt \( (Q'_s/Q'_T) \) or alveolar–arterial oxygen tension gradients (\( A–aP_{O₂} \)), reflecting the low \( V''A/Q'' \) units.

6. Apart from \( V''A/Q'' \) mismatch and hypoventilation, a low \( P_{a,O₂} \) can be caused by diffusion limitation or an anatomic shunt (either intrapulmonary or intracardiac). The hepatopulmonary syndrome (HPS), with microvascular dilatations, is an example of a low \( P_{a,O₂} \), which could be due to either or both of these causes, depending on one's point of view.

7. The passage of oxygen from terminal bronchioles to red cells is principally by molecular diffusion, the final step being chemical combination with intra-red cell Hb. The process is super-efficient, and only breaks down clinically when the surface area for exchange is reduced by alveolar destruction (a low oxygen diffusing capacity \( (D_{L,O₂}) \)) and pulmonary blood flow (\~cardiac output) is high \( (e.g. \text{on exercise}) \), giving a low \( D_{L/Q''} \) ratio.

8. The multiple inert gas elimination technique (MIGET) is a research tool for measuring \( V''A/Q'' \) distribution in a 50 compartment model of the lung, which gives insights into the pathogenesis of intrapulmonary disease.

**Keywords:** Diffusion limitation, hypoxaemia, oxygen and carbon dioxide tension in arterial blood, partial pressure at half maximum blood concentration, respiratory failure, ventilation–perfusion mismatch.

### References


