



Gas exchange and ventilation–perfusion relationships in the lung

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ABSTRACT This review provides an overview of the relationship between ventilation/perfusion ratios and gas exchange in the lung, emphasising basic concepts and relating them to clinical scenarios. For each gas exchanging unit, the alveolar and effluent blood partial pressures of oxygen and carbon dioxide (PO_2 and PCO_2) are determined by the ratio of alveolar ventilation to blood flow ($V'A/Q'$) for each unit. Shunt and low $V'A/Q'$ regions are two examples of $V'A/Q'$ mismatch and are the most frequent causes of hypoxaemia. Diffusion limitation, hypoventilation and low inspired PO_2 cause hypoxaemia, even in the absence of $V'A/Q'$ mismatch. In contrast to other causes, hypoxaemia due to shunt responds poorly to supplemental oxygen. Gas exchanging units with little or no blood flow (high $V'A/Q'$ regions) result in alveolar dead space and increased wasted ventilation, *i.e.* less efficient carbon dioxide removal. Because of the respiratory drive to maintain a normal arterial PCO_2 , the most frequent result of wasted ventilation is increased minute ventilation and work of breathing, not hypercapnia. Calculations of alveolar–arterial oxygen tension difference, venous admixture and wasted ventilation provide quantitative estimates of the effect of $V'A/Q'$ mismatch on gas exchange. The types of $V'A/Q'$ mismatch causing impaired gas exchange vary characteristically with different lung diseases.



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A review of ventilation–perfusion relationships and gas exchange, basic concepts and their relation to clinical cases <http://ow.ly/wMUwq>

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Introduction

While the healthy lung efficiently exchanges respiratory gases, hypoxaemia and hypercapnia indicate pathophysiology and failure of the lung to provide adequate gas exchange. An understanding of how gases are transferred and the causes of inefficient gas exchange are central to caring for patients with lung diseases. In this article, we will review the normal and pathological mechanisms of gas exchange. Starting with simple and building to more complex, we will emphasise basic concepts and relate them to case scenarios familiar to clinicians.

Lung structure

The structure of the lung is well suited for efficient exchange of respiratory gases. Through the airway and vascular trees, fresh gases and venous blood are delivered to and removed from a large alveolar capillary surface area. In an adult, inhaled air enters the trachea with a cross-sectional area of $\sim 3 \text{ cm}^2$ and is delivered to the alveoli with a surface area of $\sim 140 \text{ m}^2$, roughly the size of a tennis court [1]. Similarly, the pulmonary vascular tree begins as the main pulmonary artery and repeatedly bifurcates into arterioles and capillaries that cover 85–95% of the alveolar surface [1]. An exceptionally thin membrane of only $1 \mu\text{m}$ [2, 3] separates the alveolar gas and blood compartments, allowing gases to diffuse rapidly between them. Due to the relatively large blood volume within the alveolar capillaries, blood flow slows and the transit time for blood increases, normally to 0.25–0.75 s, allowing more time for gas exchange. The remarkable design that allows this gas exchanging system to be constructed within the thoracic cavity has been highlighted by comparing this engineering feat to that of folding a letter so that it fits into a thimble [3].

A single lung unit

We start with a simple lung model consisting of just one gas exchanging unit (fig. 1a). The capillaries of the unit deliver mixed venous blood with a low partial pressure of O_2 (P_{vO_2}). The partial pressure of O_2 (P_{O_2}) in the alveolar gas (P_{AO_2}) is much higher than in the capillary blood and O_2 diffuses passively from the alveolar space into the blood during passage through the capillaries (fig. 2a). The membrane separating the alveolar gas and blood compartments causes little resistance to diffusion so the P_{O_2} in end-capillary blood (P_{ecO_2}) equilibrates with P_{AO_2} well before the blood leaves the unit. Oxygenation of arterial blood is, therefore, primarily dependent on the P_{AO_2} . Note that in this idealised lung unit there is no difference between P_{AO_2} and P_{O_2} in arterial blood (P_{aO_2}). For reasons explained later, the alveolar–arterial O_2 tension difference ($P_{\text{A-aO}_2}$) is very helpful when assessing the causes of gas exchange problems in clinical medicine and we will use it throughout this review. While the term “gradient” is also commonly used, we prefer to use “difference” to highlight that the difference between the P_{AO_2} and P_{aO_2} is not due to a pressure gradient between them. The partial pressure of CO_2 (P_{CO_2}) is greater in mixed venous blood (P_{vCO_2}) than in the alveolar gas (P_{ACO_2}) and diffusion over the alveolar–capillary membrane, therefore, results in a net flow in a direction opposite to that of O_2 , from blood to alveolar gas (fig. 2b). The result is again an equal P_{CO_2} in alveolar gas and end-capillary blood (P_{ecCO_2}) because the resistance for diffusion is even less for CO_2 than for O_2 . Due to differences in the relationship between partial pressures and blood content for O_2 and CO_2 , there is approximately as much CO_2 exchanged for a partial pressure difference between mixed venous and arterial blood of 5 mmHg (0.7 kPa) as there is O_2 exchanged with a difference of 60 mmHg (6.7 kPa). The amount of O_2 carried in the blood is determined by the haemoglobin concentration, the fraction of haemoglobin binding O_2 and the P_{aO_2} (fig. 1b). When we discuss multiple lung unit models below, it is important to understand that the end-capillary blood O_2 content (C_{ecO_2}), rather than the P_{ecO_2} , from different units are additive.

Five causes of arterial hypoxaemia

A single-unit model (fig. 1a) is used to begin our discussion of five potential causes of hypoxaemia as well as hypercapnia. Our first example is one of diffusion limitation.

Diffusion limitation

In case 1, a 25-year-old male elite cyclist who undergoes a cardiopulmonary exercise study is noted to have progressively worsening arterial hypoxaemia with increasing workload (a response not seen in normal individuals). Arterial blood gases (ABGs) at end-exercise are: pH 7.18, P_{CO_2} in arterial blood (P_{aCO_2}) 30 mmHg (4.0 kPa), P_{aO_2} 81 mmHg (10.8 kPa) and arterial haemoglobin O_2 saturation 88%.

Exercise increases the amount of O_2 extracted from arterial blood in the systemic circulation, which tends to reduce P_{vO_2} . Therefore, more O_2 needs to be taken up in the lung to reach normal oxygenation of arterial blood. Exercise also increases pulmonary blood flow, which shortens the time that the blood is exposed to alveolar gas. The combined effect is that more O_2 needs to be taken up in less time (fig. 3). At very high cardiac outputs, the transit time might be too short for complete equilibration between P_{AO_2} and P_{ecO_2} . This represents diffusion limitation as a cause of hypoxaemia in athletes achieving extremely high cardiac

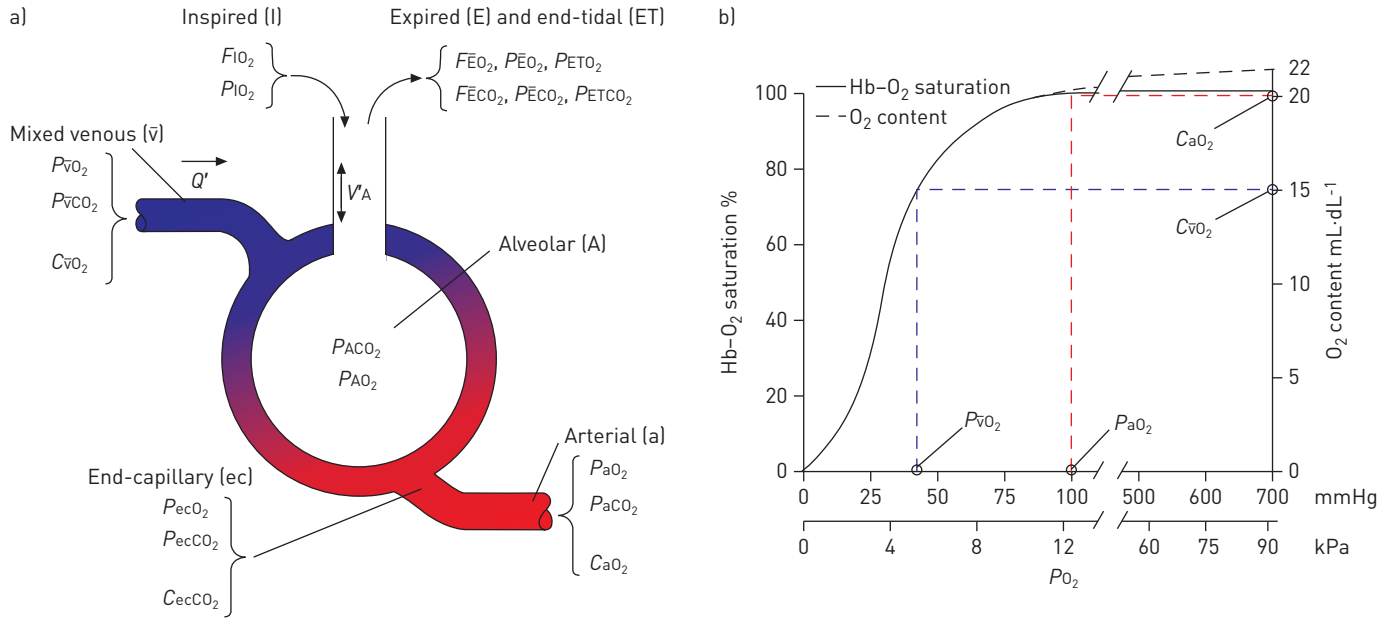


FIGURE 1 a) An illustration of the notations used for partial pressures, fractions of gas and O₂ content for different compartments in a single lung unit, as defined in table 1. Note that with a single-unit lung model, arterial and end-capillary values are equal. b) The haemoglobin–oxygen (Hb–O₂) dissociation curve for partial pressure of O₂ (P_{O₂}), O₂ saturations and O₂ content in the venous and arterial compartments for a haemoglobin concentration of 15 g·dL⁻¹.

outputs [4–6]. Hypoxaemia due to diffusion limitation can also be seen in normal individuals during exercise at altitude. In this setting, the driving pressure for O₂ diffusion is decreased due to the lower P_{O₂} in inspired air (P_IO₂) at altitude and the transit time of blood through the alveolar capillaries is shorter due to higher cardiac outputs. A diffusion limitation can also occur in patients with interstitial lung diseases. Patients with these diseases might have a normal P_{aO₂} at rest but develop hypoxaemia during exercise, which can be explained by the combined effect of increased resistance to diffusion through the thickened alveolar–capillary membrane, reduced P_{vO₂} and a shortened transit time [7].

Diffusion limitation is one of five causes of hypoxaemia (table 2). The lack of equilibration between P_{AO₂} and P_{ecO₂} creates an increased P_{A–aO₂}. Hypoxaemia in these patients, as a rule, responds nicely to supplemental O₂. While this does not correct the diffusion limitation, it raises the P_{AO₂} and the driving

TABLE 1 Glossary of gas variables and other notations

Variable	Definition and (units)	Possible compartments X	Examples of gas Y
P _{XY}	Partial pressure of gas Y in compartment X (mmHg or kPa)	B = barometric	O ₂
F _{XY}	Fraction of gas Y in compartment X (decimal or %)	I = inspired gas	CO ₂
C _{XY}	Content of gas Y in compartment X (mL per 100 mL of blood)	E = expired gas	H ₂ O
S _{xO₂}	Haemoglobin–oxygen saturation in compartment X [%]	Ē = mixed expired gas ET = end-tidal A = alveolar gas a = arterial blood c = capillary ec = end-capillary blood v̄ = mixed venous blood	
V _x	Ventilation (mL·min ⁻¹) in compartment X	A = alveolar D = dead space	
Q _x	Blood flow (mL·min ⁻¹) in compartment X	t = total s = shunt	
V _A /Q _x	Regional ratio of alveolar ventilation to perfusion (unitless)		
V _x	Volume (mL) in compartment X	T = tidal D = dead space	

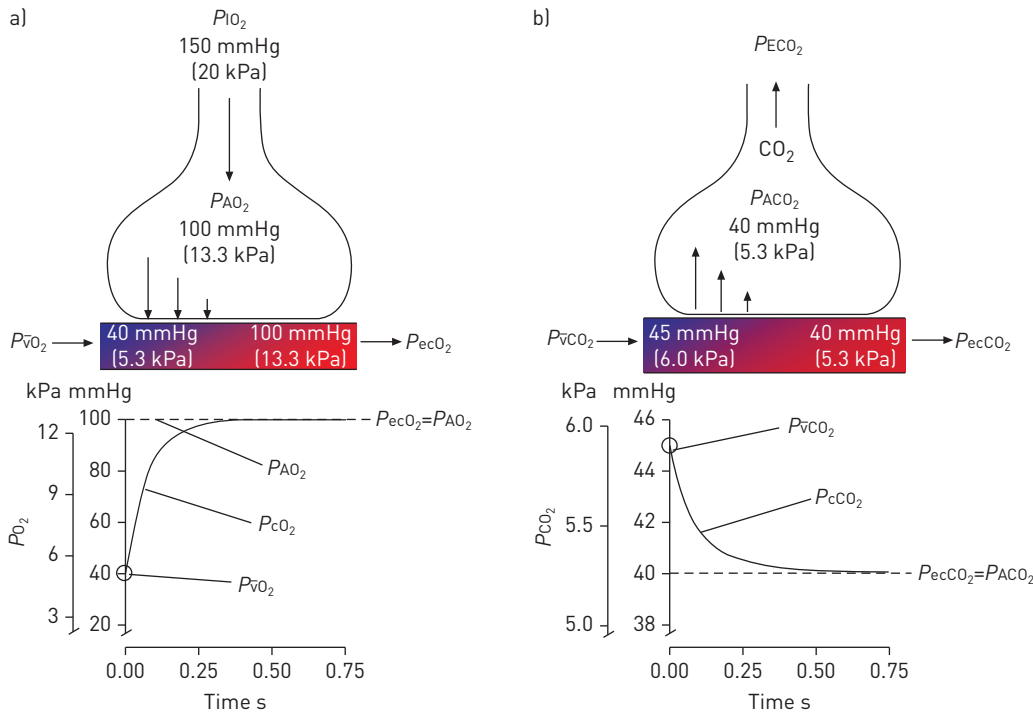


FIGURE 2 a) P_{O_2} in different compartments and how diffusion of O_2 along the capillary allows P_{ecO_2} to equal P_{AO_2} well before the blood leaves the unit. Note that the result is a P_{A-aO_2} of zero. b) PCO_2 illustrated in a similar manner. The time scale on the diagrams in both panels refers to the transit time for the erythrocytes through the alveolar capillaries, normally 0.25–0.75 s. For a glossary of terms, see table 1.

pressure for diffusion of O_2 into the blood. Due to the low resistance to diffusion of CO_2 , P_{aCO_2} is normal in patients with O_2 diffusion limitations. Although diffusion limitation is our first cause listed for hypoxaemia in table 2, from a clinical perspective, it is an uncommon reason for a low P_{aO_2} .

Hypoventilation

In case 2, an 82-year-old female with chronic renal failure on continuous ambulatory peritoneal dialysis (CAPD) had recently contracted whooping cough from her grandchildren. Her physician prescribed an

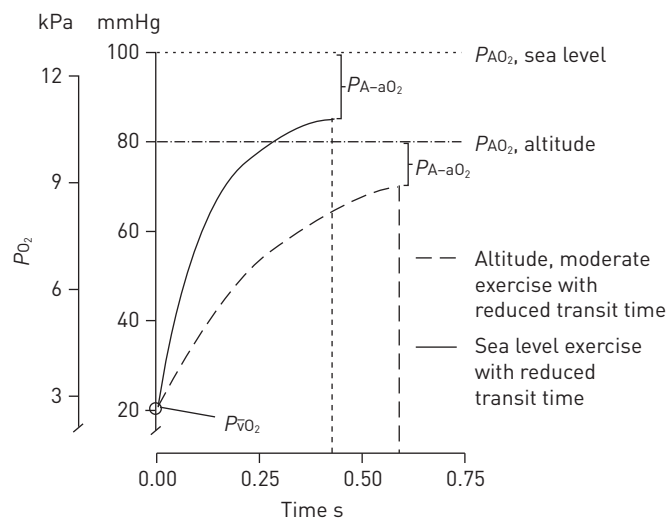


FIGURE 3 Oxygenation of capillary blood as a function of time under different conditions. The panel illustrates how P_{ecO_2} and hence P_{aO_2} fail to reach P_{AO_2} due to low P_{vO_2} and short transit time during extreme exercise at sea level (solid curve) and moderate exercise at altitude (dashed curve). Compare with the normal rate of oxygenation in figure 2a. For a glossary of terms, see table 1.

TABLE 2 Five causes of hypoxaemia

Cause of hypoxaemia	PAO_2	$PA-aO_2$	PaO_2 response to increased F_{iO_2}
Diffusion limitation	Normal	Increased	Improved
Hypoventilation	Reduced	Normal	Improved
Decreased P_{iO_2}	Reduced	Normal	Improved
Low $V'A/Q'$	Reduced locally	Increased	Improved
Shunt	Reduced locally	Increased	Minimal improvement

PAO_2 : alveolar partial pressure of O_2 ; $PA-aO_2$: alveolar–arterial O_2 tension difference; PaO_2 : arterial partial pressure of O_2 ; F_{iO_2} : inspiratory O_2 fraction; P_{iO_2} : partial pressure of O_2 in inspired gas; $V'A/Q'$: ratio of alveolar ventilation to perfusion.

opioid-containing antitussive to reduce the cough. She is now drowsy and unable to manage the CAPD routines. An ABG analysis reveals pH 7.17, PaO_2 45 mmHg (6.0 kPa) and $PaCO_2$ 77 mmHg (10.3 kPa).

This case highlights hypoventilation as a cause of hypoxaemia. Although the quantitative relationship is complex [8, 9], it can be intuitively understood that PAO_2 in our single alveolar unit (fig. 1a) is influenced by the ratio between O_2 delivery (ventilation, $V'A$) and O_2 removal (blood flow, Q'). Hence, one of the determinants of PAO_2 is the balance or ratio between ventilation and blood flow ($V'A/Q'$). In the patient from case 2, hypoventilation and normal blood flow results in a low $V'A/Q'$ ratio (less delivery and unchanged removal of O_2), which lowers PAO_2 and consequently P_{ecO_2} . Conversely, hyperventilation (increased ventilation relative to blood flow) increases PAO_2 and P_{ecO_2} . $PACO_2$ is also determined by the $V'A/Q'$ ratio but CO_2 is delivered through blood flow and CO_2 is removed through ventilation, the converse of O_2 . Hence, a decreased $V'A/Q'$ ratio results in higher $PACO_2$ and $PaCO_2$, the hallmark of hypoventilation, while an increased ratio lowers $PACO_2$. These relationships are illustrated in figure 4. The balance between O_2 delivery and removal results in a PAO_2 that can be quantified using the alveolar gas equation (box 1).

Hypoxaemia secondary to hypoventilation is, thus, due to a low PAO_2 and is the second cause of a low PaO_2 listed in table 2. Because there is no impairment of gas exchange across the alveolar–capillary membrane,

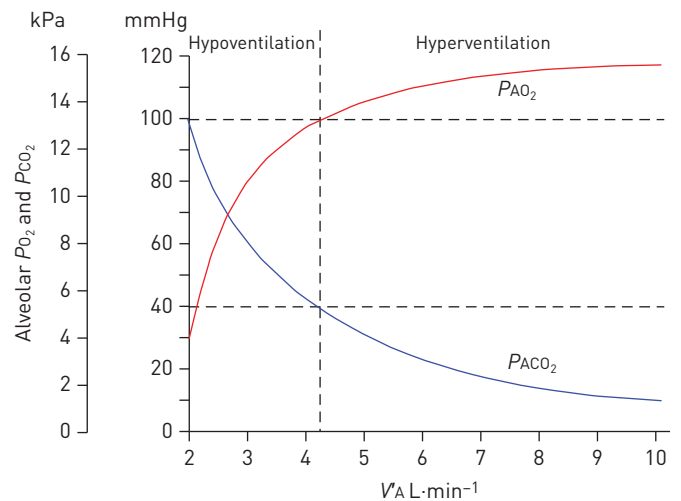


FIGURE 4 The effects of hyper- and hypoventilation on the PAO_2 (red) and $PACO_2$ (blue) and, therefore, also on PaO_2 and $PaCO_2$ if no other $V'A/Q'$ mismatch is present. The dashed lines indicate normal values for $V'A$, PAO_2 and $PACO_2$. The diagram is derived assuming unchanged cardiac output, O_2 consumption and CO_2 production with mixed venous values changing with changes in PaO_2 and $PaCO_2$. With hypoventilation, P_{vO_2} and P_{vCO_2} are lower and higher than normal, respectively. Note that changes in $V'A$ correspond to changes in $V'A/Q'$ ratio since blood flow (cardiac output) is held constant. Thus, decreased ventilation (low $V'A/Q'$ ratio) causes PAO_2 and $PACO_2$ to move toward the mixed venous values while hyperventilation shifts PAO_2 and $PACO_2$ toward their inspired values. Hypoventilation, thus, results in both hypoxaemia and hypercapnia. An increase in F_{iO_2} results in an upward shift of the PO_2 curve while the PCO_2 curve remains fixed. In this situation, $PaCO_2$ might be high even in the absence of hypoxaemia. For a glossary of terms, see table 1. Adapted from [10].

PAO_2 and PaO_2 are similarly decreased and the $PA-aO_2$ is normal in hypoxaemia due to hypoventilation alone. In case 2, the alveolar gas equation (box 1) results in an estimated PAO_2 of 53 mmHg (7.1 kPa) and $PA-aO_2 \sim 7$ mmHg (0.9 kPa), a normal value. Hypoxaemia due to hypoventilation can be resolved with supplemental O_2 , increasing PAO_2 even if hypoventilation remains uncorrected. One important aspect of O_2 treatment in this situation is that hypoventilation, while breathing air, will result in severe hypoxaemia before $PaCO_2$ increases to dangerously high levels. In contrast, providing supplemental O_2 can result in PAO_2 and PaO_2 being maintained above 90 mmHg (12 kPa) even with hypoventilation causing severe hypercapnia. A clinically important corollary is that a normal pulse oximetry reading in a patient breathing air is a good indication of adequate ventilation (normal $PaCO_2$). However, when a patient is on supplemental O_2 , a normal O_2 saturation cannot be used to judge the adequacy of ventilation.

Low inspiratory oxygen pressure

In case 3, a 21-year-old very fit, mountaineer notices, while ascending Mont Blanc (4810 m), that her fingers are blue and that her haemoglobin O_2 saturation is 65%.

Although the fraction of O_2 in air is always 0.21, decreasing barometric pressure at high altitude causes a proportional decrease in the PIO_2 . Using the alveolar gas equation (box 1), an appropriate barometric pressure for her altitude (420 mmHg (56 kPa)), no change in ventilation ($PaCO_2$ 40 mmHg (5.3 kPa)) and an R of 0.8 results in an expected PAO_2 at the top of Mont Blanc of ~ 28 mmHg (3.7 kPa) and severe hypoxaemia. Low PIO_2 , at high altitude or when breathing an inspiratory O_2 fraction (FI_{O_2}) < 0.21 , is therefore one additional cause of hypoxaemia. Again, gas exchange at the alveolar–capillary membrane is normal. The cause of hypoxaemia is reduced PAO_2 and consequently the $PA-aO_2$ is normal. How is it then possible to ascend Mont Blanc? Hypoxaemia increases the respiratory drive, thereby increasing the total $V'A/Q'$ ratio and O_2 delivery to the alveoli, which partially corrects PAO_2 and PaO_2 (fig. 3). Increased ventilation results in hypocapnia, defined as $PaCO_2 < 40$ mmHg (< 5.3 kPa). Recent ABG samples from climbers breathing air at the summit of Mount Everest revealed a mean PaO_2 of 25 mmHg (3.3 kPa) and $PaCO_2$ of 13 mmHg (1.7 kPa) [11]. A second method to raise PAO_2 and improve PaO_2 is to breathe supplemental O_2 . Most mountaineers reaching the summit of Mount Everest use supplemental O_2 .

Two-unit lung models

For the two remaining causes of hypoxaemia, both examples of $V'A/Q'$ mismatch, we must shift to multi-unit lung models. While fascinating in its design and gas exchange capacity, the anatomical structure of the lung with multiple parallel gas exchanging units sets the stage for non-uniform and different distributions of regional ventilation and blood flow. If regional ventilation and perfusion are not perfectly matched, *i.e.* each unit is not receiving equal proportions of total blood flow and total ventilation, $V'A/Q'$ ratios will vary between lung regions, each of them will have different PAO_2 and $PACO_2$ and gas exchange will be less efficient. Figure 5 shows the range of PAO_2 and $PACO_2$ seen in units as a function of their $V'A/Q'$ ratio. To demonstrate how gas exchange becomes less efficient with units of differing V'/Q' ratios, we will begin with a simple two-unit lung model.

BOX 1 Two versions of the alveolar gas equation

$$P_{AO_2} = P_{IO_2} - \frac{P_{aCO_2}}{R} = F_{IO_2} \times (P_B - P_{H_2O}) - \frac{P_{aCO_2}}{R}$$

$$P_{AO_2} = P_{IO_2} - \frac{P_{aCO_2}}{R} \times [1 - F_{IO_2}(1 - R)]$$

The alveolar equation exists in several forms; the upper version is easier to remember and is used in clinical practice. The lower version is more accurate because it corrects for the difference in inspiratory and expiratory minute volume when the respiratory exchange ratio, R, does not equal 1.0. The equation is used to calculate the alveolar–arterial O_2 difference ($PA-aO_2$). In the absence of diffusion limitation, $V'A/Q'$ mismatch and shunt (see text), PaO_2 equals PAO_2 . The $PA-aO_2$ can, therefore, be used as a measure of the overall deviation from perfect gas exchange.

PIO_2 : partial pressure of O_2 in inspired gas reaching the alveoli, calculated as $PIO_2 = F_{IO_2} \times (P_B - P_{H_2O})$; F_{IO_2} : fraction of O_2 in inspired gas; P_B : barometric pressure; P_{H_2O} : saturated vapour pressure of water at body temperature, 47 mmHg (6.3 kPa) at 37°C; R: the respiratory exchange ratio defined as the ratio between the amount of CO_2 and O_2 exchange.

P_B must be known or estimated for the appropriate altitude; at sea level it is commonly estimated at 760 mmHg (101.3 kPa). If not measured, R is usually assumed to be 0.8. Using these values at sea level, the O_2 concentration in air (F_{IO_2} 0.21) and a normal $PaCO_2$ of 40 mmHg (5.3 kPa) the upper equation results in PAO_2 of 100 mmHg (13.3 kPa).

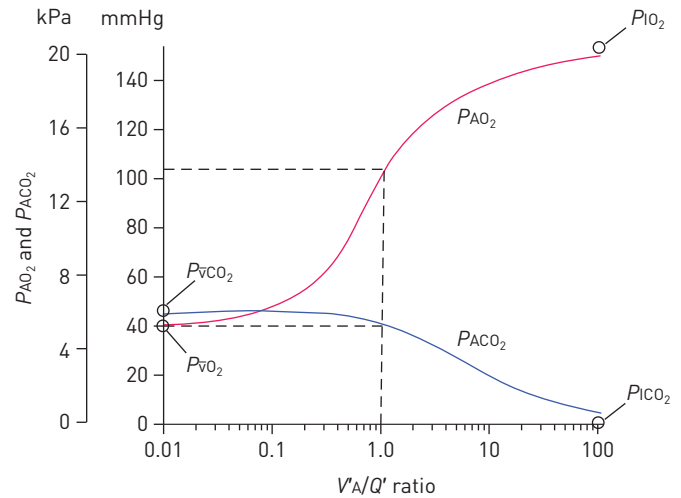


FIGURE 5 Diagram showing how PAO_2 and $PACO_2$ vary with the $V'A/Q'$ ratio under the assumption of normal values for P_{IO_2} (150 mmHg (20 kPa)), P_{VO_2} (40 mmHg (5.3 kPa)) and P_{vCO_2} (45 mmHg (6 kPa)). These assumptions are not realistic for a whole lung since changes in PAO_2 and $PACO_2$ will cause secondary changes in mixed venous values (fig. 4 is more realistic in this regard), but the diagram illustrates the influence of the $V'A/Q'$ ratio on alveolar and end-capillary partial pressures for regional lung units in a situation when total ventilation to blood flow is sufficient to maintain normal mixed venous values. Note that a decreased $V'A/Q'$ ratio below the normal value of ~ 1 results in a sharp fall in PAO_2 and a lesser increase in $PACO_2$, with both approaching the mixed venous values shown farthest to the left. An increased $V'A/Q'$ ratio causes PAO_2 to increase and $PACO_2$ to decrease, approaching the inspired values shown farthest to the right. For a glossary of terms, see table 1. Adapted from [10].

Low $V'A/Q'$ units

In case 4, a 67-year-old female with severe emphysema has an ABG of pH 7.35, PaO_2 55 mmHg (7.3 kPa) and $PaCO_2$ 55 mmHg (7.3 kPa) when breathing air. With supplemental O_2 at $3 \text{ L}\cdot\text{min}^{-1}$, haemoglobin O_2 saturation improves from 87% to 93% on pulse oximetry.

Figure 6 illustrates uniform distribution of blood flow but uneven distribution of ventilation to two units, such that one unit has a $V'A/Q'$ ratio of 2.0 while the other unit has a ratio of 0.1. The low $V'A/Q'$ ratio results in low PAO_2 in this unit and, thus, lower O_2 content and P_{ecO_2} for blood leaving this unit. Note that the effect is analogous to that in the patient who was hypoventilating in case 2, but in this case it relates to only a part of the lung. The nearly complete oxygenation of haemoglobin at a normal $V'A/Q'$ ratio means that the relative over-ventilation (high $V'A/Q'$ ratio) of the other unit results in only a slightly increased O_2 content for blood leaving this unit. Also remember that the O_2 content of arterial blood (CaO_2) is determined by the flow-weighted mean of the O_2 contents, not partial pressures, for blood from different units. The overall effect of low $V'A/Q'$ units is, therefore, a reduced PaO_2 and an increased $PA-aO_2$. Low $V'A/Q'$ units are, thus, the fourth cause of hypoxaemia (table 2). The effect of low $V'A/Q'$ units on $PACO_2$ is less compared with the effect on PAO_2 , because CO_2 elimination is increased in the unit with a high $V'A/Q'$ ratio. In patients with low $V'A/Q'$ regions, hypercapnia is also prevented by the ventilatory response to increased $PaCO_2$. Because low $V'A/Q'$ regions are in fact ventilated, the detrimental effect on arterial oxygenation can be counteracted by increasing the F_{IO_2} , which increases PAO_2 , even in low $V'A/Q'$ regions. Low $V'A/Q'$ units, therefore, cannot be the sole cause of hypoxaemia in patients that fail to respond to increased F_{IO_2} .

Shunt

In case 5, a 32-year-old male with severe acute respiratory distress syndrome (ARDS) secondary to bacterial pneumonia has an ABG on mechanical ventilation with an F_{IO_2} of 0.80 that reveals pH 7.28, PaO_2 67 mmHg (8.9 kPa) and $PaCO_2$ 61 mmHg (8.1 kPa).

Figure 7 shows a situation in which one unit is without any ventilation, hence it cannot participate in gas exchange. Blood flow through this unit, therefore, constitutes an intrapulmonary shunt. Shunt can be viewed as one extreme of the range of $V'A/Q'$ ratios with a ratio of 0. End-capillary blood flow from this unit has the same P_{ecO_2} and C_{ecO_2} as mixed venous blood and when combined with blood from the other unit decreases oxygenation of arterial blood. Shunt is, therefore, the fifth and last cause of hypoxaemia (table 2). The CaO_2 is again the flow-weighted average of O_2 content from the gas exchanging unit (C_{ecO_2}) and the shunted blood ($C_{c'O_2}$) (fig. 7). The amount of shunt is quantified as the fraction of cardiac output ($Q's/Q't$) distributed to nonventilated units (box 2). The effect on arterial oxygenation depends on this

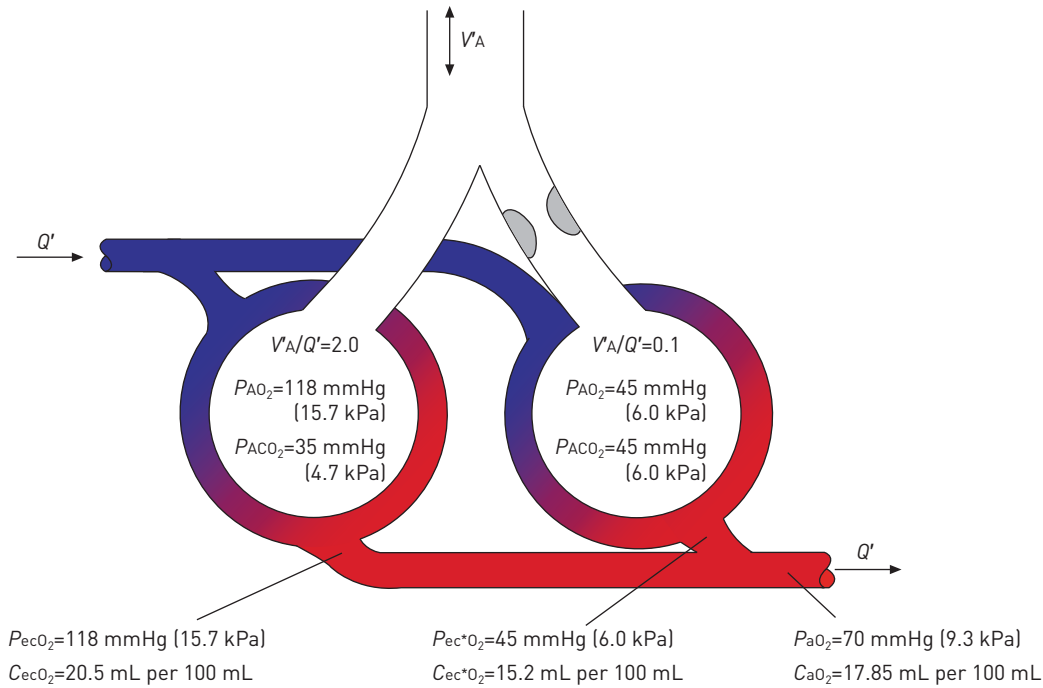


FIGURE 6 Low V_A/Q' represented by a two-unit model in which blood flow is the same to both units but ventilation is different, resulting in units with V_A/Q' ratios of 2.0 and 0.1. Note that different V_A/Q' ratios result in PAO_2 and $PACO_2$ being very different between the two units. The CaO_2 is a flow-weighted average from the two units, in this case identical to the arithmetic means because flow is equal between the units. The PaO_2 is determined from the normal haemoglobin O_2 saturation *versus* PO_2 curve assuming a haemoglobin concentration of $15 \text{ g}\cdot\text{dL}^{-1}$ (fig. 1b). For a glossary of terms, see table 1, ec and ec* denotes end-capillary blood from the two different units.

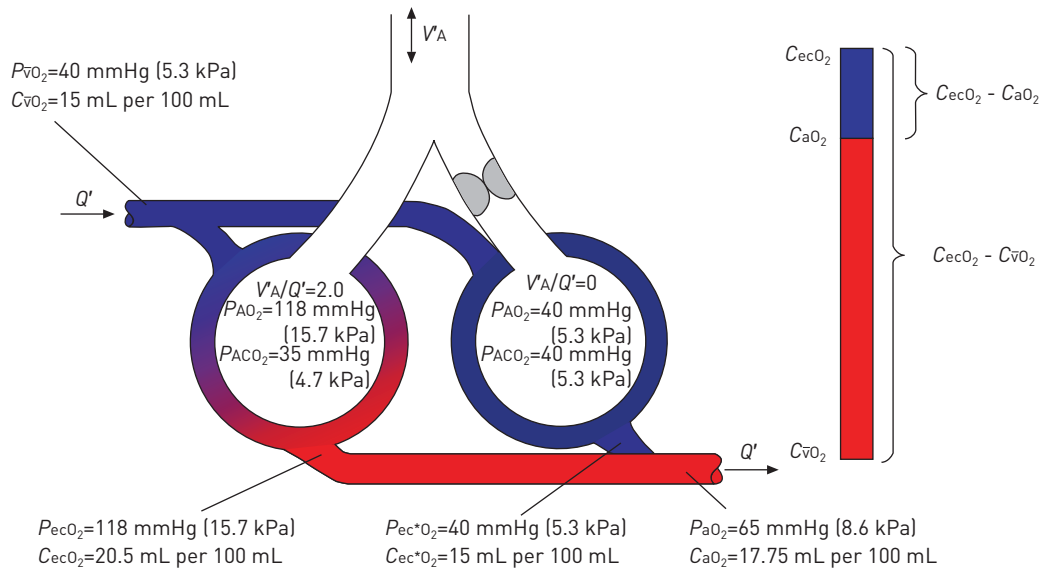


FIGURE 7 Shunt represented by a two-unit model in which blood flow is the same to both units but there is no ventilation to one unit. Note that alveolar and end-capillary PO_2 and PCO_2 in the nonventilated unit equal the mixed venous values because there is no gas exchange in this unit. The CaO_2 is a flow-weighted average of C_{ecO_2} and $C_{ec^*O_2}$ from the two units, or the arithmetic mean when flow is equal between the units as in this example. The PaO_2 is determined from the normal haemoglobin O_2 saturation *versus* PO_2 curve assuming a haemoglobin concentration of $15 \text{ g}\cdot\text{dL}^{-1}$ (fig. 1b). The vertical bar to the right is a visual representation of the shunt equation (see box 2 and the later section on venous admixture). For a glossary of terms, see table 1, ec and ec* denotes end-capillary blood from the two different units.

BOX 2 The shunt equation

$$\frac{Q'_s}{Q'_t} = \frac{C_{ecO_2} - C_{aO_2}}{C_{ecO_2} - C_{\bar{v}O_2}}$$

The shunt equation quantifies the amount of blood in the three-compartment model that reaches the left heart without exchanging any gases. The equation quantitates venous admixture as a fraction of total lung blood flow, *i.e.* cardiac output. Breathing an F_{IO_2} of 1.0 can be used to eliminate the impact of low $V'A/Q'$ units and, thus, calculate the true shunt. The equation is derived from principles of mass conservation, see for example [12] and figure 7. Notations are explained in table 1. C_{aO_2} and $C_{\bar{v}O_2}$ are obtained from samples of arterial and mixed venous blood, respectively; the latter requires a pulmonary artery catheter. C_{ecO_2} is calculated assuming that P_{ecO_2} equals that of ideal alveolar gas according to the alveolar gas equation. This equation can be conceptualised and graphically presented as shown in the vertical bar of figure 7. C_{ecO_2} at the top of the bar is the best the C_{aO_2} could be if there is no shunt at all. $C_{\bar{v}O_2}$ at the bottom of the bar is the worst the C_{aO_2} could be if all of the blood flow was through a shunt. The resultant C_{aO_2} is somewhere between the $C_{\bar{v}O_2}$ and the C_{ecO_2} . The fraction of blood flow through the shunt (Q'_s/Q'_t) is, therefore, the observed difference between the C_{ecO_2} and C_{aO_2} divided by the potential greatest difference between C_{ecO_2} and $C_{\bar{v}O_2}$.

fraction and the O_2 content of mixed venous blood ($C_{\bar{v}O_2}$). For a shunt of a certain magnitude, lower $C_{\bar{v}O_2}$ will result in worse arterial oxygenation. Interventions aimed at increasing mixed venous O_2 saturation ($S_{\bar{v}O_2}$) (and consequently $C_{\bar{v}O_2}$), such as raising the C_{aO_2} through increased haemoglobin concentration, decreasing O_2 consumption or increasing cardiac output, might therefore improve hypoxaemia caused by a large shunt. The shunt fraction has, however, been shown to increase with increasing cardiac output [13, 14]; such interventions might therefore be less effective than expected. Increased $P_{\bar{v}O_2}$ and increased pulmonary arterial pressure, which may decrease and counteract hypoxic vasoconstriction (discussed later), are speculative explanations for this effect of cardiac output on shunt.

In contrast to the situation with low $V'A/Q'$ regions, with shunt increasing F_{IO_2} is much less effective at improving arterial oxygenation. With increasing shunt fraction, the effect of raising F_{IO_2} is progressively less and for very large shunts, even an F_{IO_2} of 1.0 has little effect on P_{aO_2} . The reasons for the small effect are that raised F_{IO_2} fails to improve P_{AO_2} in unventilated units and that the little extra O_2 that can be added to blood flow through ventilated units is not enough to offset the impact of the shunted blood. The relationships between the variables shunt size, F_{IO_2} and P_{aO_2} are illustrated by the iso-shunt diagram (fig. 8). Examples of clinical conditions with hypoxaemia due to large intrapulmonary shunts are extensive atelectasis, severe pneumonia and ARDS. In these conditions, the shunt might exceed 50% of total lung blood flow [13, 16–19]. An intracardiac right-to-left shunt has the same effect on P_{aO_2} as an intrapulmonary shunt. Even in normal

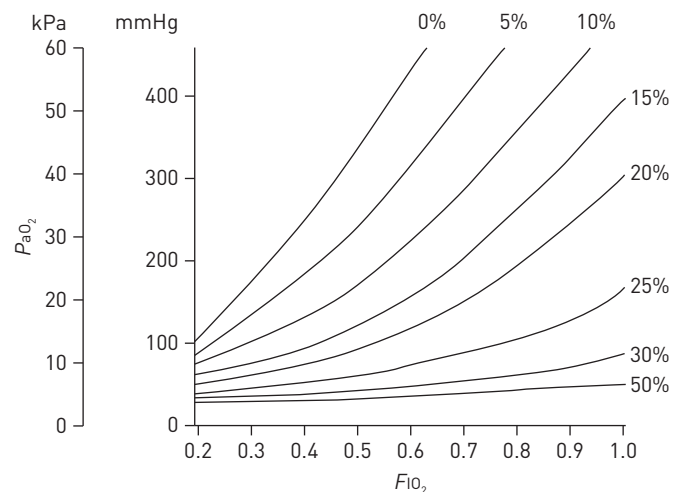


FIGURE 8 The iso-shunt diagram, illustrating the relationship between P_{aO_2} and F_{IO_2} in the presence of a shunt corresponding to different percentages of total lung blood flow. Note the near linear relationship between P_{aO_2} and F_{IO_2} in the absence of shunt. With increasing shunt fractions, the change in P_{aO_2} with increasing F_{IO_2} is much more flat. Hence, a large increase in F_{IO_2} results in little change in P_{aO_2} . For a shunt >30% of cardiac output, even a F_{IO_2} of 1.0 fails to result in a P_{aO_2} of 100 mmHg (13.3 kPa). Modelling is based on a haemoglobin concentration of $14 \text{ g}\cdot\text{dL}^{-1}$, P_{aCO_2} of 40 mmHg (5.3 kPa) and an arterial–mixed venous oxygen content difference ($C_{a-\bar{v}O_2}$) of $5 \text{ mL}\cdot\text{dL}^{-1}$. For a glossary of terms, see table 1. Adapted from [15].

BOX 3 Physiological dead space (Bohr) equation

$$\frac{V_D}{V_T} = \frac{P_{aCO_2} - P_{\bar{E}CO_2}}{P_{aCO_2}}$$

V_D is the physiological dead space or wasted ventilation in the three-compartment model. The equation is derived from mass balance calculations that use the alveolar partial pressure of carbon dioxide (P_{ACO_2}), which is here replaced with P_{aCO_2} [20]. On exhalation, the P_{ACO_2} from well perfused lung regions is diluted by the lack of CO_2 from the units of dead space. The degree to which the $P_{\bar{E}CO_2}$ is reduced below the P_{aCO_2} is, thus, proportional to the amount of dead space. This concept is embodied in the vertical bar of figure 9, where the P_{aCO_2} is at the top of the bar and represents the $P_{\bar{E}CO_2}$ if there is no dead space at all. The P_{iCO_2} at the bottom of the bar represents the $P_{\bar{E}CO_2}$ if the entire lung were dead space. The resultant $P_{\bar{E}CO_2}$ is between these two values. The fraction of wasted ventilation (V_D/V_T) is, therefore, the observed difference between P_{aCO_2} and $P_{\bar{E}CO_2}$ divided by the potential greatest difference between P_{aCO_2} and P_{iCO_2} . Because P_{iCO_2} is zero, the denominator reduces to P_{aCO_2} alone. For a glossary of terms, see table 1.

subjects, P_{aO_2} is less than P_{AO_2} due primarily to a right-to-left shunt of 2–3% of cardiac output. Most of this is not a strict intrapulmonary shunt but represents venous blood added to arterial blood from bronchial veins and the Thebesian veins of the left ventricle [12]. The effect of shunt on CO_2 exchange is discussed in box 3.

Dead space

In a continuation of case 4, the 67-year-old female with severe emphysema is hospitalised with an acute exacerbation of chronic obstructive pulmonary disease (COPD). ABG reveals pH 7.21, P_{aO_2} 67 mmHg (8.9 kPa) and P_{aCO_2} 85 mmHg (11.3 kPa). Measurements reveal she is breathing $12 \text{ L}\cdot\text{min}^{-1}$.

Despite a minute ventilation (V'_E) that is about twice what is normal at rest, this patient presents with an elevated P_{aCO_2} , indicating hypoventilation. How can this be explained? With each inspiration, in all subjects, part of the tidal volume (V_T) is retained in the conducting airways and, therefore, fails to contribute to gas exchange. This volume corresponds to the anatomical dead space, and is $\sim 150 \text{ mL}$ ($2\text{--}3 \text{ mL}\cdot\text{kg}^{-1}$) or one third of a normal V_T [12, 21]. A normal dead space fraction of the tidal volume (V_D/V_T) is therefore ~ 0.3 . Figure 9 illustrates two units that are equally ventilated but one of the units is without blood

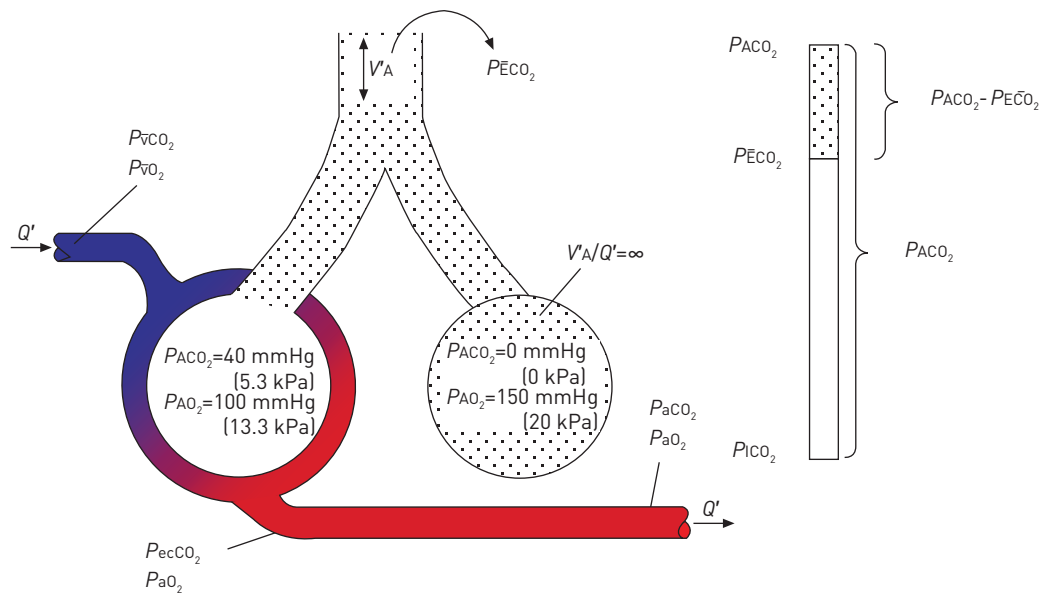


FIGURE 9 Alveolar dead space illustrated by a two-unit model in which there is blood flow to only one unit while there is ventilation to both units. Because no gas exchange occurs in the unit without blood flow, PAO_2 and P_{ACO_2} in this unit equal the inspired pressures. The dead space unit does not affect arterial blood gases because there is no blood flow contribution from this unit. The lack of CO_2 expired from the dead space region dilutes the concentration of CO_2 expired from the other unit and expired PCO_2 is thus lower than from perfused units. The degree by which the expired PCO_2 is decreased in comparison with P_{aCO_2} is proportional to the fraction of the lung that is dead space. The vertical bar to the right is a visual representation of the dead space equation (box 3). It is analogous to that in figure 7 and explained in the section on wasted ventilation. For a glossary of terms, see table 1.

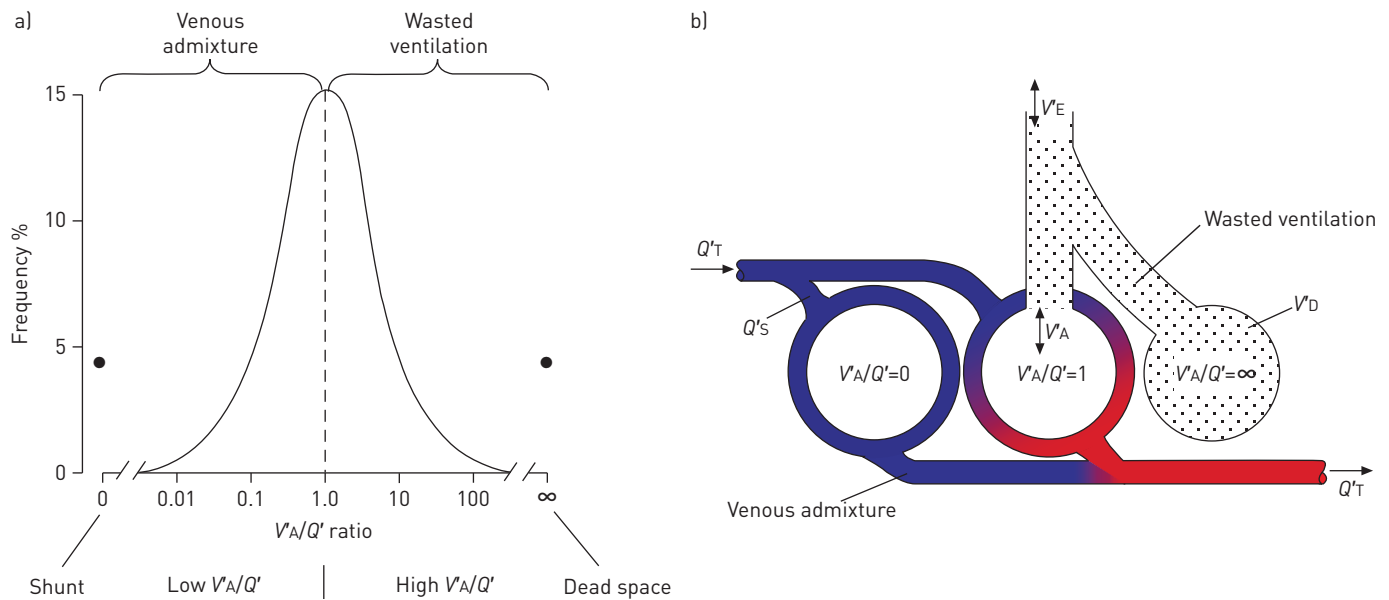


FIGURE 10 a) Percentage of lung units (vertical axis) with different V_A/Q' ratios (horizontal axis) in a lung that has an overall V_A/Q' of 1.0 (minute ventilation is the same as cardiac output). Overall gas exchange efficiency is determined by the spread of units across different ratios, with optimal efficiency corresponding to a very narrow distribution with all units having a ratio of 1.0. The curve illustrates the normal situation with most units having a ratio close to optimal. Units to the left of the dashed line have a low ratio and, therefore, contribute to increased P_{A-aO_2} and venous admixture; the effect increases with increasing deviation from a ratio of 1.0. Units to the right of the dashed line have a high ratio and, therefore, contribute to wasted ventilation; again the effect increases with increasing deviation from a ratio of 1.0. Shunt and dead space units are plotted at the two extremes of the horizontal axis. b) Illustration of the three-compartment model proposed by RILEY and COURNAND [9] to quantify V_A/Q' mismatch as venous admixture and wasted ventilation. For a glossary of terms, see table 1.

flow and, therefore, constitutes alveolar dead space. One clinical cause might be pulmonary embolism. Alveolar dead space refers to gas exchanging units that are ventilated but without blood flow and the V_A/Q' ratio is infinite. Apparatus dead space refers to the volume of any face mask, tubing, *etc.* that functions as an extension of the anatomical dead space. Total dead space (V_D), therefore, consists of summed anatomical dead space, alveolar dead space and any apparatus dead space.

Minute ventilation refers to the total volume of expired gas per minute, while effective alveolar ventilation refers to the volume of gas per minute that participates in gas exchange. In contrast, dead space ventilation, or wasted ventilation, is the fraction of total ventilation that does not contribute to gas exchange. This fraction of wasted ventilation is often expressed as the ratio V_D/V_T . Effective alveolar ventilation can be calculated as $V'_A = RR \times (V_T - V_D)$, where RR is respiratory rate, or as $V'_A = V'_E \times (1 - V_D/V_T)$. Note that effective alveolar ventilation is determined by both minute ventilation and V_D/V_T . Increased V_D inherently means that a greater minute ventilation is needed to maintain effective alveolar ventilation adequate for CO_2 removal. An increase in V_D/V_T without a compensatory increase in minute ventilation results in decreased P_{aO_2} and increased P_{aCO_2} . In the patient in case 4, the high minute ventilation is not enough to compensate for the increased V_D/V_T , which results in hypercapnia. Increased P_{aCO_2} might also be seen in those sedated and mechanically ventilated patients who do not increase their minute ventilation in the setting of a new pulmonary embolism.

High V_A/Q' units

High V_A/Q' units are units that are overventilated in proportion to blood flow, for example, a unit that receives a ventilation of $1 \text{ L} \cdot \text{min}^{-1}$ but a blood flow of only $0.1 \text{ L} \cdot \text{min}^{-1}$ resulting in a V_A/Q' ratio of 10. Although this unit does not represent alveolar dead space, ventilation in excess of blood flow causes a “dead space effect”, because less CO_2 will be removed by ventilation of a high V_A/Q' unit than by ventilation of a better perfused region. Thus, similar to alveolar dead space, addition of high V_A/Q' units means that a greater minute ventilation is needed to maintain adequate gas exchange. High V_A/Q' regions are primarily due to areas of normal ventilation with low blood flow. The impact of these regions on ABGs is small, because the contribution of any region to ABG composition is flow-weighted.

More than two-unit lung models

So far we have focused on models with one or two lung units. In reality, gas exchange within the entire lung and the resulting P_{aO_2} and P_{aCO_2} are determined by the effluent blood flow from thousands of units with

different $V'A/Q'$ ratios (fig. 10). RILEY and COURNAND [9] suggested that the effect of $V'A/Q'$ mismatch on gas exchange can be more simply thought of and quantified as a lung consisting of only three compartments with different $V'A/Q'$ ratios: one compartment with ideal $V'A/Q'$ matching ($V'A/Q'=1.0$), one totally without ventilation ($V'A/Q'=0$, shunt) and one without blood flow ($V'A/Q'=\infty$, dead space).

The model is practical because it is relatively easy to obtain the measurements needed to quantify shunt blood flow and dead space ventilation (discussed below). It is important to understand that the calculations assume that the effects of $V'A/Q'$ mismatch on P_{aO_2} and P_{aCO_2} are entirely due to shunt and dead space ventilation, and that all gas exchange occurs in units with ideal $V'A/Q'$ matching. The model does not reflect the true situation as it ignores gas exchange in units with other $V'A/Q'$ ratios.

Venous admixture

With the three-compartment model, shunt blood flow is calculated using the shunt equation (box 2). The calculated shunt, alternatively and more accurately described as venous admixture, corresponds to the amount of right-to-left shunt of mixed venous blood that would result in the observed arterial oxygenation in the absence of low $V'A/Q'$ regions. Venous admixture might, therefore, be increased even in the absence of true shunt.

Using values obtained while breathing 100% O_2 can differentiate hypoxaemia due to low $V'A/Q'$ regions from the effect of a true shunt, because the venous admixture from low $V'A/Q'$ regions is abolished in this situation [12]. One problem with this approach is that breathing 100% O_2 tends to increase the amount of shunt due to absorption atelectasis so the degree of shunt while breathing a lower F_{IO_2} might be overestimated. Shunt can also be measured using inert gases with low solubility in blood [17, 22]. It should be noted that this methodology also differs from the calculation of venous admixture as it excludes the shunt effect of venous blood added to arterial blood after the passage through the lung, from Thebesian and bronchial veins.

Wasted ventilation (physiological dead space)

According to the three-compartment model of RILEY and COURNAND [9], physiological dead space or wasted ventilation corresponds to the total dead space that would cause the observed impairment of CO_2 elimination (box 3). We prefer the term “wasted ventilation”, since it better describes the meaning of this quantity. In normal lungs, the wasted ventilation closely corresponds to the anatomical dead space. In addition to anatomical dead space, wasted ventilation also results from any apparatus, alveolar dead space and high $V'A/Q'$ units. Blood from shunt regions will have a P_{eCO_2} equal to the mixed venous value, which raises P_{aCO_2} and thereby the calculated wasted ventilation; this has been coined shunt dead space [21]. This is an effect of using P_{aCO_2} as a surrogate for P_{ACO_2} ; hence, while not an effect of increased dead space or high $V'A/Q'$ regions, it does represent impaired CO_2 elimination [23]. As discussed above, effective alveolar ventilation equals minute ventilation minus wasted ventilation. A minute ventilation of $7.5 \text{ L}\cdot\text{min}^{-1}$ and a normal V_D/V_T of 0.3 results in an effective alveolar ventilation of $5.25 \text{ L}\cdot\text{min}^{-1}$. Chronic lung disease might increase V_D/V_T to ≥ 0.8 ; in this case, a minute ventilation of $\geq 25 \text{ L}\cdot\text{min}^{-1}$ is required for an effective alveolar ventilation of $5 \text{ L}\cdot\text{min}^{-1}$. Measures of wasted ventilation, thus, estimate the effect of $V'A/Q'$ mismatch on the minute ventilation needed to maintain adequate gas exchange. Although not measured, for the patient in case 4, the increased P_{aCO_2} despite a high minute ventilation is most likely explained by a greater component of wasted ventilation.

Because the control of breathing aims to maintain a normal P_{aCO_2} , an increase in wasted ventilation requires an increased minute ventilation to maintain unchanged effective alveolar ventilation. The first consequence of increased wasted ventilation in most situations is, therefore, not an increase in P_{aCO_2} but a change in minute ventilation and, therefore, the work of breathing. Chronic hypercapnia can be viewed as an adaptive response as it means that CO_2 removal can be maintained with a lower minute ventilation and, thus, lessens the work of breathing.

The arterial to end-tidal P_{CO_2} difference

The physiological dead space equation (box 3) uses the difference between P_{aCO_2} and the P_{CO_2} of mixed expired gas (P_{ECO_2}) to calculate the total fraction of wasted ventilation. By contrast, the difference between P_{aCO_2} and the P_{CO_2} of mixed expired alveolar gas excludes the effect of anatomical and apparatus dead space and, therefore, estimates the extent of high $V'A/Q'$ and alveolar dead space regions. Because the last part of the exhaled V_T consists of alveolar gas (box 4), the end-tidal P_{CO_2} (P_{ETCO_2}) can be used as a surrogate measure of mixed P_{ACO_2} . The $P_{aCO_2}-P_{ETCO_2}$ difference, therefore, correlates with dead space and wasted ventilation [28–30]. It is noteworthy that, remembering the physiological dead space equation, modelling studies have shown that $(P_{aCO_2}-P_{ETCO_2})/P_{aCO_2}$ has a more linear correlation with alveolar dead space fraction than the simpler $P_{aCO_2}-P_{ETCO_2}$ [29, 30]. Although dependent on, for example, age, the inhaled/

BOX 4 End-tidal PCO_2 ($PETCO_2$)

At expiration, the first part of the exhaled gas originates from the anatomical dead space where no gas exchange occurs. Therefore, this gas has the same PCO_2 as inspired gas, usually close to zero (fig. 11). After a short transitional phase consisting of a mixture of anatomical dead space and alveolar gas, the rest of the expiration consists of mixed alveolar gas. Measurement of PCO_2 of exhaled gas at the end of the expiration, $PETCO_2$, has been used as a measure of mixed alveolar gas and as a noninvasive measure of $PaCO_2$. There are, however, several considerations with this approach. In diseased lung the proportion of airflow from different lung regions might change during expiration, with different regions emptying sequentially rather than in parallel. In this situation, late emptying of low $V'A/Q'$ regions with a high $PaCO_2$ causes the PCO_2 to increase throughout expiration and potentially be greater than the mean $PaCO_2$ at the end of exhalation [24]. Even with healthy lungs, a similar phenomenon occurs when breathing with large tidal volumes during exercise [25, 26]. In this case, one important cause is that $PaCO_2$ increases during the course of expiration due to more CO_2 being added to alveolar gas [27]. In these situations $PETCO_2$ might in fact even be greater than $PaCO_2$, the upper limit being the $PvCO_2$ [24, 25]. Obviously, a $PETCO_2$ greater than the mixed $PaCO_2$ will cause the $PaCO_2$ - $PETCO_2$ to underestimate wasted ventilation.

exhaled gas volume and mode of ventilation, a $PaCO_2$ - $PETCO_2 < 5$ mmHg (0.7 kPa) is considered normal [31, 32] and is supported by $PETCO_2$ being close to 36 mmHg (4.8 kPa) in a small number of normal subjects [33]. $PaCO_2$ - $PETCO_2$ has been shown to correlate with alveolar dead space fraction and alveolar recruitment in animal models of ARDS [34]. $PETCO_2$ is illustrated in figure 11 and further discussed in box 4.

The combined effect of low and high $V'A/Q'$ regions

In comparison with optimal $V'A/Q'$ matching, redistribution of either regional ventilation or blood flow must result in both low and high $V'A/Q'$ regions. For example, a shift in blood flow from one unit to another will cause one unit to be less perfused in proportion to ventilation (high $V'A/Q'$) and the other unit to be more perfused in proportion to ventilation (low $V'A/Q'$). Compared with the effect on PaO_2 , the effect of $V'A/Q'$ mismatch on $PaCO_2$ is often more obvious because 1) the numerical changes in PaO_2 are larger than those in $PaCO_2$ and 2) impaired CO_2 elimination is often counteracted by increased minute ventilation which offsets the effect of $V'A/Q'$ mismatch on $PaCO_2$ to a much greater degree than the effect on PaO_2 . The net effect of $V'A/Q'$ mismatch is always reduced gas exchange efficiency and for a given FIO_2 and minute ventilation results in lower PaO_2 and higher $PaCO_2$ than would have occurred if $V'A/Q'$ matching were optimal.

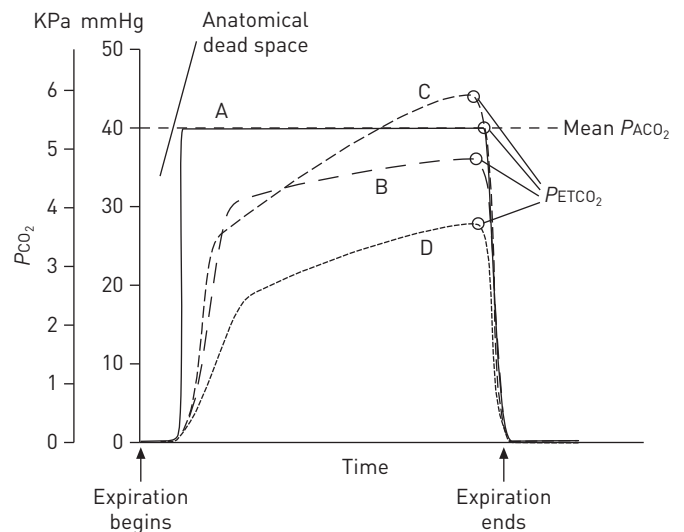


FIGURE 11 Capnogram showing the PCO_2 of exhaled gas (vertical axis) plotted versus time (horizontal axis) during a single exhalation. Curve A corresponds to a theoretical curve from a single lung unit model in which the first part of the exhalation consists solely of anatomical dead space gas without CO_2 and the rest of the exhaled alveolar gas has a uniform PCO_2 that is equal to $PaCO_2$. In this single-unit model, $PETCO_2 = PaCO_2 = PaCO_2$. Curve B corresponds to a capnogram from a healthy individual with a normal amount of $V'A/Q'$ mismatching. Note that there would be a small difference between the $PETCO_2$ (marked with an open circle) and $PaCO_2$. Curve C illustrates how increased $V'A/Q'$ causes the PCO_2 of exhaled gas to increase throughout expiration. In this case $PETCO_2$ even exceeds $PaCO_2$ and possibly $PaCO_2$. While this is not common, it can occur with slow exhalation of a large VT or at maximal exercise. Curve D illustrates a situation with increased alveolar dead space, resulting in an increased difference between $PaCO_2$ and $PETCO_2$, as might be seen in a patient with a pulmonary embolism. For a glossary of terms, see table 1.

V'A/Q' mismatch in the normal lung

Regional ventilation and blood flow are not uniform in the normal lung. Heterogeneities of ventilation and perfusion have been attributed to the influence of airway and vascular tree geometries as well as regional differences in blood flow and lung compliance due to gravity [35–39]. The traditional zone model [38] of perfusion and ventilation predicts that both perfusion and ventilation increase in the gravitational direction, from apex to lung base in the upright posture. However, they do not increase at the same rate, and $V'A/Q'$ tends to decrease from apex to base. Animal studies using higher spatial resolution measurements have suggested a fractal model [40, 41], in which asymmetries in the vascular tree result in perfusion heterogeneities that cannot be explained by the hydrostatic gradient due to gravity. Regional ventilation and blood flow are further influenced by posture, lung volume and application of positive airway pressures [36, 37, 42], to name just a few factors. Despite these non-uniformities, efficient gas exchange is possible through the close matching of ventilation and blood flow, attributed to the shared influences of structure and gravity [35]. The correlation is, however, not perfect, which causes $V'A/Q'$ ratios and, therefore, PAO_2 and $PACO_2$, to vary between different lung regions [35].

In young healthy individuals, most ventilation and blood flow are distributed to units with $V'A/Q'$ ratios between 0.3 and 2.0 [22], which tends to result in a range of PAO_2 from about 90 mmHg to 130 mmHg (fig. 5) [43]. With increasing age, ventilation and blood flow are distributed to units with a wider range of $V'A/Q'$ ratios, with blood flow to low $V'A/Q'$ regions being attributed to reduced ventilation of dependent lung regions due to airway closure [12, 44]. Consequently, $PA-aO_2$ increases with age [12, 44].

Assessing arterial oxygenation

Several indices are used to evaluate PaO_2 in relation to FiO_2 . When breathing air, the $PA-aO_2$ provides a sensitive measure of gas exchange efficiency but is dependent on age. A number of different studies have sampled relatively small numbers of individuals in different populations to determine the distribution of $PA-aO_2$ in normal individuals [45–48]. In all studies, the mean $PA-aO_2$ increases with age, as do the confidence intervals around the mean. Table 3 incorporates data from two of the larger populations [45, 46]. A simplified formula for the normal $PA-aO_2$ when breathing air is (age in years/4)+4 mmHg (divide result by 7.5 for kPa). Because the normal $PA-aO_2$ is primarily due to venous admixture, increasing FiO_2 raises PAO_2 more than PaO_2 and the normal value for $PA-aO_2$ increases with increasing FiO_2 . The PaO_2/FiO_2 ratio is more frequently used in clinical practice and in the definition of ARDS. A lower limit for normal PaO_2 when breathing air of 80 mmHg (10.7 kPa) corresponds to a normal PaO_2/FiO_2 ratio being >400 mmHg (53 kPa), while diagnosing ARDS requires a PaO_2/FiO_2 <300 mmHg (40 kPa). The PaO_2/FiO_2 is also dependent on the FiO_2 , level of positive end-expiratory pressure (PEEP) and the arterial venous O_2 extraction [49, 50] and is, therefore, a difficult measure to interpret. The PaO_2/FiO_2 is not helpful in differentiating between different causes of hypoxaemia.

V'A/Q' mismatch and vascular tone

Hypoxic pulmonary vasoconstriction

Hypoxic pulmonary vasoconstriction (HPV) causes pre-capillary vasoconstriction in units with low PAO_2 (<60 mmHg (8.0 kPa)), such as those with low $V'A/Q'$ or shunt [51–54]. The effect of HPV is to divert blood flow away from hypoxic units toward better ventilated units, improving $V'A/Q'$ matching and arterial

TABLE 3 PaO_2 and $PA-aO_2$ at different ages

Age years	Mean PaO_2		Lower 95th percentile of PaO_2		Mean $PA-aO_2$		Upper 95th percentile of $PA-aO_2$	
	mmHg	kPa	mmHg	kPa	mmHg	kPa	mmHg	kPa
18–24	99.9	13.3	91.1	12.1	2.0	0.3	11.4	1.5
25–34	99.8	13.3	91.7	12.2	3.3	0.4	7.4	1.0
35–44	98.3	13.1	85.8	11.4	4.7	0.6	17.1	2.3
45–54	97.0	12.9	83.8	11.2	6.5	0.9	17.1	2.3
55–64	90.2	12.0	82.8	11.0	12.1	1.6	18.2	2.4
>64	88.7	11.8	71.1	9.5	14.8	2.0	29.3	3.9
Males >70	77.0	10.3	62.0	8.3	25.2	3.4	40.4	5.4
Females >70	73.5	9.8	59.6	7.9	28.1	3.7	41.3	5.5

PaO_2 : arterial partial pressure of O_2 ; $PA-aO_2$: alveolar–arterial O_2 tension difference. Data from [45, 46].

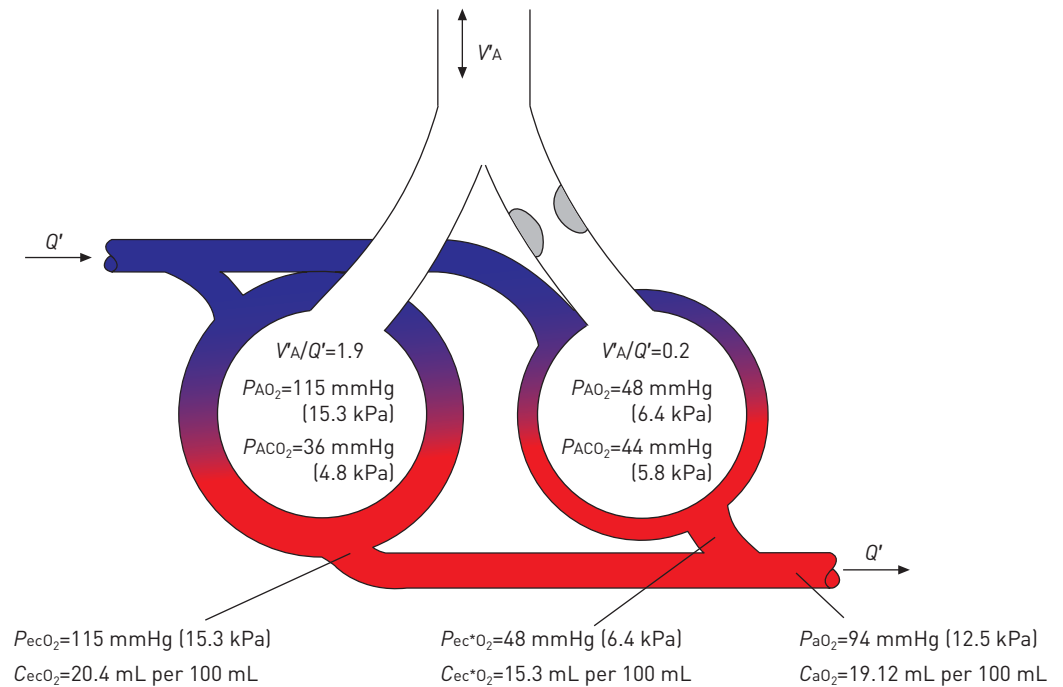


FIGURE 12 Hypoxic pulmonary vasoconstriction (HPV) occurs in lung regions with low PAO_2 , effectively redistributing blood flow away from the hypoxic regions and towards better oxygenated regions. The distribution of ventilation is identical to that in figure 6 but blood flow to the low $V'A/Q'$ unit is halved due to HPV. Compare with figure 6 to see the effect of this redistribution of blood flow on gas exchange. Because ventilation is not altered, the $V'A/Q'$ ratios change such that the hypoxic region has an increased $V'A/Q'$ ratio, increasing the PAO_2 in that region. With more blood flow coming from the well ventilated region, with the higher PAO_2 , CaO_2 and PaO_2 are markedly improved. For a glossary of terms, see table 1, ec and ec* denotes end-capillary blood from the two different units.

oxygenation (fig. 12). For example in humans, HPV reduces blood flow to atelectatic regions by $\sim 50\%$ [55, 56]; the beneficial effect on arterial oxygenation can be deduced from moving from one iso-shunt line to another at a fixed FIO_2 in the iso-shunt diagram (fig. 8). The efficacy of HPV in correcting $V'A/Q'$ mismatch decreases with the extent of the hypoxic lung region [53, 57]. One example is low PAO_2 within the entire lung (e.g. due to severe hypoventilation or high altitude). In this case, generalised vasoconstriction raises pulmonary arterial pressure without improving $V'A/Q'$ matching. Animal and human experiments indicate that HPV is of little importance for $V'A/Q'$ matching in normal lungs [53, 58, 59]. By contrast, HPV can be of critical importance in patients with disease causing regional alveolar hypoxia [53], improving PaO_2 by up to 20 mmHg (2.7 kPa) in patients with COPD or ARDS [54]. An illustration of the importance of HPV is that systemically administered vasodilators, inhibiting HPV, might reduce PaO_2 in such patients [60].

Supplemental oxygen and carbon dioxide retention in COPD patients

One further illustration of the clinical importance of HPV is its role in O_2 -induced hypercapnia in patients with COPD. Although often attributed to a decreased drive to breathe, it has been shown that administration of supplemental O_2 to these patients can increase $PaCO_2$ despite constant minute ventilation [61, 62]. The major explanation is that supplemental O_2 raises the PAO_2 in low $V'A/Q'$ units, inhibiting regional HPV and increasing blood flow to these units. Consequently, blood is diverted away from better ventilated regions, converting them to high $V'A/Q'$ units, which increases wasted ventilation [61, 62]. This is an illustration of how increased wasted ventilation decreases effective alveolar ventilation (discussed above), despite unchanged minute ventilation. In addition, because the low $V'A/Q'$ units have a higher $PACO_2$, the restored blood flow to these units results in more CO_2 being delivered to the arterial blood. Increased $V'A/Q'$ mismatch as the dominant mechanism causing O_2 -induced hypercapnia remains, however, controversial: other work has shown that decreased minute ventilation can contribute to increased $PaCO_2$ [63]. One further explanation is the Haldane effect, in which increased PaO_2 decreases binding of both H^+ and CO_2 to haemoglobin, thereby increasing the amount of physically dissolved CO_2 and, thus, PCO_2 [12, 64]. In other words, for any given CO_2 content, PCO_2 will be higher with greater haemoglobin O_2 saturation. The Haldane effect has been estimated to explain 6–78% of the increase in $PaCO_2$ in COPD patients after administration of supplemental O_2 [61, 65, 66].

Inhaled vasodilators

Inhaled vasodilators can be used to improve $V'A/Q'$ mismatch. The concept is that inhaled vasodilators are distributed to each region in proportion to regional ventilation and well ventilated regions are, therefore, more vasodilated. Locally reduced vascular tone causes a shift in blood flow away from unventilated regions toward the better ventilated regions, improving $V'A/Q'$ matching and gas exchange. Inhaled nitric oxide has been shown to reduce shunt [60, 67] and improve arterial oxygenation in patients with ARDS [60, 68, 69]. A similar effect has been demonstrated with inhaled prostacyclin [70, 71]. Interestingly, the effect is less consistent in patients with COPD. In this case, inhaled nitric oxide can result in both improved and worsened gas exchange; the latter can be explained by the vasodilator also reaching low $V'A/Q'$ regions. Inhibition of HPV increases blood flow to these low $V'A/Q'$ regions, which causes further arterial desaturation [67, 72]. The beneficial effect of inhaled nitric oxide might, therefore, be less consistent in hypoxaemia caused by low $V'A/Q'$ regions than in conditions characterised by shunt regions.

$V'A/Q'$ mismatch in lung diseases

COPD

Patients with COPD might present with hypoxaemia, hypercapnia or both. Hypoxaemia is primarily explained by perfusion of underventilated (low $V'A/Q'$) regions, which has been attributed to airway disease [73–76]. Shunt is of little importance in the absence of complicating conditions such as pneumonia or atelectasis [7, 74] and hypoxaemia is, therefore, expected to respond to increased PiO_2 . Hypercapnia is explained by decreased effective alveolar ventilation due to increased wasted ventilation secondary to high $V'A/Q'$ regions and alveolar dead space caused by emphysematous destruction of the lung parenchyma [73–75]. Hypercapnia becomes evident only when the patient is unable to maintain the added work of breathing required for adequate alveolar ventilation. Changes in cardiac output, O_2 consumption and minute ventilation have been shown to modulate the effect of increased $V'A/Q'$ mismatch in patients with acute COPD exacerbations [74].

ARDS

Gas exchange in patients with ARDS, often caused by pneumonia or sepsis, is characterised by severe hypoxaemia due to loss of aeration of large lung regions. Several studies have shown that arterial hypoxaemia in these patients is mostly caused by shunt blood flow that might exceed 50% of cardiac output [13, 16–19]. Low $V'A/Q'$ regions are either absent or a lesser cause of low PaO_2 [16, 17]. Impaired diffusion does not seem to contribute to arterial hypoxaemia [16]. The effect of PEEP on $V'A/Q'$ mismatch in these patients is especially interesting. PEEP has been shown to reduce the amount of nonaerated lung tissue through alveolar recruitment and to improve arterial oxygenation through a decrease in shunt blood flow [13, 16, 17, 19, 77, 78]. Increased PEEP has also been shown to increase total dead space, which is interpreted as an increased number of unperfused alveoli secondary to increased airway pressure with compression of alveolar capillaries in nondependent lung regions [16, 77–79]. The effect of PEEP on dead space is attenuated if the negative effect of PEEP on cardiac output is counteracted by fluid loading to increase cardiac preload, which also illustrates that reduced cardiac output might increase V_D/V_T [79]. By contrast, PEEP in combination with alveolar recruitment has been shown to decrease wasted ventilation [80]. When using PEEP to optimise gas exchange in these patients it is, thus, necessary to balance the potential beneficial and detrimental effects on oxygenation, wasted ventilation and cardiac output. Another tool to improve gas exchange in ARDS patients is treatment in the prone posture. Animal experiments and clinical studies have demonstrated that the prone posture decreases shunt and $V'A/Q'$ mismatch, improving arterial oxygenation [81–83]. A recent clinical trial demonstrated that the use of the prone posture early in the course of ARDS was associated with improved survival [84]. The primary mechanism postulated to increase survival is not improved gas exchange, but a more uniform distribution of regional ventilation resulting in less ventilator-induced lung injury [83, 85].

Pulmonary embolism

Pulmonary embolism results in lung regions with no or reduced blood flow (high $V'A/Q'$ regions) and, thus, increased wasted ventilation. Less obviously, redistribution of blood flow to other lung regions causes these regions to become relatively overperfused, and transformed into low $V'A/Q'$ regions, creating hypoxaemia and an increased $PA-aO_2$. The reason for hypoxaemia is, thus, increased $V'A/Q'$ mismatch but not increased shunt [86, 87]. The effect on ABGs is modified by the respiratory response to increased $PaCO_2$, the end result often being a dyspnoeic patient with hypoxaemia and normal or even low $PaCO_2$. Hypoxaemia might be aggravated by circulatory failure causing low CvO_2 or by intracardiac right-to-left shunting, both provoked by acute pulmonary hypertension. Importantly, the absence of hypoxaemia or increased $PA-aO_2$ does not rule out pulmonary embolism [88, 89]. Similarly, using the $PaCO_2-PETCO_2$ to gauge wasted ventilation is informative, but in isolation is not definitive for diagnosing pulmonary embolism [90]. While

a $PETCO_2$ measurement indicating increased wasted ventilation increases the likelihood of pulmonary embolism [91] and a normal amount of wasted ventilation diminishes the likelihood [33, 92], the utility of these measures is very dependent on the *a priori* clinical probability of pulmonary embolism in the individual patient [90] and the fraction of the pulmonary vascular tree that is involved [91].

Summary

- 1) There are five cause of hypoxaemia. Decreased P_{aO_2} can be caused by hypoventilation, low P_{iO_2} , diffusion limitation, low $V'A/Q'$ regions or shunt. In contrast with other causes, hypoxaemia due to shunt characteristically responds poorly to increased F_{iO_2} . Low $V'A/Q'$ regions and shunt are by far the most common causes of clinically encountered hypoxaemia.
- 2) Hypoventilation and low $V'A/Q'$ regions also impair CO_2 removal, but the magnitude of the effect on P_{aCO_2} is less and modified by the ventilatory response to hypercapnia.
- 3) High $V'A/Q'$ regions and alveolar and apparatus dead space cause increased wasted ventilation and, thus, impaired CO_2 elimination. The primary response to increased wasted ventilation is, in most situations, increased minute ventilation and work of breathing, not increased P_{aCO_2} .
- 4) The effect of $V'A/Q'$ mismatch on gas exchange efficiency can be quantified using calculations of P_{A-aO_2} , venous admixture and wasted ventilation.
- 5) Low and high $V'A/Q'$ regions cause hypoxaemia, impaired CO_2 elimination and increased work of breathing in COPD patients.
- 6) Shunt is the most important cause of hypoxaemia in patients with ARDS and pneumonia.

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