

## CHAPTER 4

# The Respiratory System

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All living cells have an absolute requirement for a regular supply of energy. Energy is usually handled in the form of the molecule adenine triphosphate (ATP), a product of a series of metabolic reactions within the mitochondria of each cell together referred to as *respiration*. A fuel such as glucose is the only essential substrate for respiration. However, the efficiency of the process is increased by up to eight times in the presence of  $O_2$ , which ultimately takes the role of an oxidising agent. The provision of  $O_2$  to the mitochondria, and the removal of the waste product of respiration,  $CO_2$ , are therefore essential for life. This chapter considers how these two goals are achieved at the level of the whole organism.

The process of delivering  $O_2$  to and removing  $CO_2$  from the body may be split into three: transporting the gases into and out of the organism, getting the substance to or from the active cells within the organism and finally getting the substance to or from the mitochondria within each cell. In organisms such as bacteria where surface area to volume ratio is large and distances within the organism are small, simple diffusion is sufficient to solve these problems. This same strategy is used to supply  $O_2$  to the human cornea. However, in larger multicellular organisms such as humans, distances are ordinarily limiting. We therefore require a dedicated organ, the lungs, to provide a large surface area over which gas exchange can occur. Furthermore, we also require a specialised circulatory system, the bloodstream, to carry these gases around the body. We will begin by discussing the transport of gases into and out of the lungs, then focus on the exchange of gases between the lungs and the blood before finally considering

how these gases are carried in the blood. The transport of this blood to the tissues is dealt with in Chapter 5.

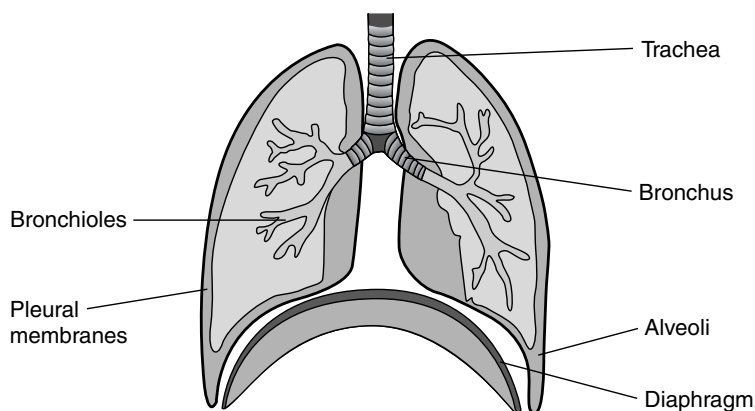
## 4.1 The Transport of Gases into and out of the Lungs

All fluids, whether liquids or gases, will flow from regions of high pressure to regions of low pressure (see Appendix). It follows that in order for air to enter the lungs when we breathe in (*inspiration*), the pressure in the lungs must fall below atmospheric pressure. Conversely, in order for waste gases to leave when we breathe out (*expiration*), the pressure must rise above atmospheric pressure. This is achieved by using a property of gases which is described by Boyle's law. This states that "the pressure exerted by a fixed amount of an ideal gas at a constant temperature is inversely proportional to its volume". Although the gas mixture in the lungs is not ideal, most importantly because each molecule of gas has a finite volume, the principle is still approximately true and means that an increase in lung volume leads to a predictable decrease in pressure within the air spaces. Conversely, a decrease in lung volume leads to an increase in pressure. The consequence of this is that in order to generate the pressure changes needed to force air to flow into and out of the lungs, a change in lung volume is all that is needed.

Before we can begin to understand how these changes in volume are brought about, we first need to consider what determines lung volume at rest, i.e. at the end of expiration.

### 4.1.1 The respiratory system at rest

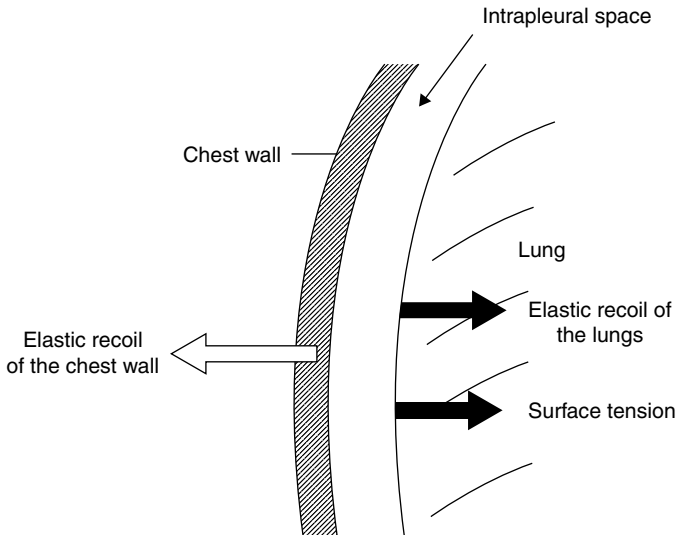
As Fig. 40 shows, the lungs are in a sealed chamber, the thorax. Both the lungs and the chest wall are covered by thin membranes, the *parietal* and *visceral pleuras* respectively. The narrow space between the pleuras, the *intrapleural space*, is filled with a thin layer of fluid. Strong cohesive forces generated by attractive intermolecular forces in this fluid pull the two layers of pleura together. Thus the pleural fluid ensures that if a force acts on the chest wall then it also acts on the lungs: if the volume of the thorax increases, so does the volume of the



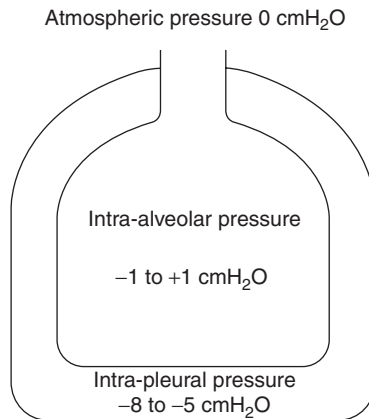
**Fig. 40.** The respiratory system.

lungs, and vice versa (try pulling two wet microscope slides apart). It is fair to wonder why it is necessary to have an intrapleural space filled with fluid and not instead simply have the lungs fixed to the chest wall. This might seem a particularly good alternative when we later consider the potentially devastating consequences of air entering the intrapleural space (*pneumothorax*). However, the fluid allows the pleural membranes to slide over each other as lung volume changes, greatly reducing friction forces and therefore resistance.

The lungs and the chest wall form a closed system which is in equilibrium at rest. The total inward forces must therefore equal the total outward forces, i.e. the net force acting is zero (Fig. 41). Two forces act on the lungs: a force pulling inwards due to the elastic tension in the lung tissue, which at equilibrium is stretched, and another force pulling inwards due to the surface tension in the alveoli, which we will discuss in more detail later. Both these forces tend to make the lungs collapse. These inward forces are balanced by an outward force due to the elastic tension in the chest wall, which at equilibrium is compressed. The end result is that the lungs and chest wall are pulled away from each other. This increases the volume of the intrapleural space and results in the intrapleural pressure being negative (Fig. 42).



**Fig. 41.** Forces acting on the lungs and chest wall.



**Fig. 42.** Pressures in the respiratory system.

#### 4.1.2 *Pressure changes during breathing*

So far we have shown that it is the balance of inward and outward forces acting on the lungs and chest wall which define their volumes at rest. The same forces are responsible for changes in volume: increasing

**Clinical Box 10: Pneumothorax**

If the intrapleural space becomes connected with either the atmosphere outside or with the alveoli, air will tend to enter down its pressure gradient. This can occur as a result of trauma or disease and is known as a *pneumothorax*. When this occurs, the intrapleural pressure becomes positive and, since there is no longer a force to counteract the elastic tendency of the lung to shrink, it collapses. The lung will remain collapsed until the negative intrapleural pressure is restored. If the defect is temporary, most small pneumothoraces will eventually resolve on their own as the air within the intrapleural space is gradually absorbed by capillaries surrounding the lung. However, in a sick patient with significant air in this space, a *chest drain* may be needed. In essence, one end of a tube is introduced into the intrapleural space and the other is placed under the surface of water. The water acts a valve, allowing air to escape from the intrapleural space on expiration when the pressure in the thorax exceeds atmospheric pressure, but preventing it from entering during inspiration.

the volume of the thorax increases the volume of the intrapleural space, making the intrapleural pressure more negative, increasing the outward force on the lungs and increasing lung volume.

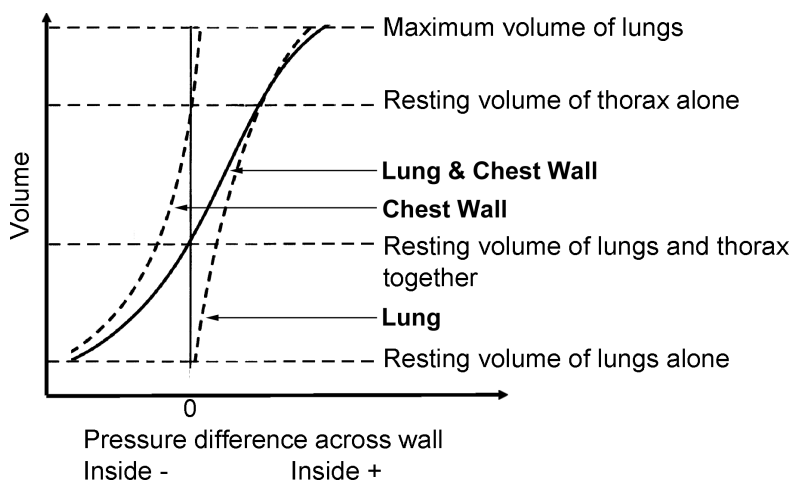
This increase in the volume of the thorax is achieved by contracting the muscular diaphragm, which forms the base of the chest cavity, and the external intercostal muscles between the ribs, which form the walls of the cavity. The result is that during quiet inspiration the volume of the intrapleural space increases and the intrapleural pressure decreases from  $-5 \text{ cmH}_2\text{O}$  at end-expiration to  $-8 \text{ cmH}_2\text{O}$  at end-inspiration. This in turn leads to an increase in lung volume and a decrease in the intra-alveolar pressure from  $0 \text{ cmH}_2\text{O}$  to  $-1 \text{ cmH}_2\text{O}$ . Air then flows down its energy gradient into the lungs until intra-alveolar pressure reaches zero at end-inspiration and air flow stops.

Conversely, expiration requires an increase in alveolar pressure above atmospheric pressure. During quiet expiration, this occurs passively as the lungs and chest wall recoil: the intra-alveolar pressure reaches a maximum of around +1 cmH<sub>2</sub>O before again falling to zero. Thus during quiet inspiration and expiration, the pressure in the alveoli only varies between -1 cmH<sub>2</sub>O and +1 cmH<sub>2</sub>O. These very small pressure changes are all that is needed to produce the necessary changes in lung volume because the pressures are applied, and therefore the forces act, over the entire surface of the lung. This is in sharp contrast to the situation when patients are mechanically ventilated through tubes inserted into their upper airways. Then, pressure changes can only be applied at the end of the tube and these must be conducted along the airways to the lungs. The end result is that far larger pressures are needed for mechanical ventilation than normal ventilation.

### 4.1.3 Compliance

We can now begin to consider the importance of the physical properties of the respiratory system. We will begin with the lungs and chest wall. The stretchiness of the lungs and chest wall are usually quantified as *compliance*, the change in volume per unit change in pressure. This is represented by the gradients of the *static volume pressure curves* show in Fig. 43. To construct such static curves, data points are constructed by stopping breathing at a range of lung volumes and measuring the difference between the pressure at the mouth (atmospheric pressure) and the pressure in the intrapleural space (approximated as the intra-oesophageal pressure). Notably, the compliance of the lungs and chest wall added together is less than the compliance of either individually. As the curves show, compliance is not constant but rather changes with volume. This is because the stretchiness of both the lungs and chest wall changes as they are stretched, just as an elastic band becomes less stretchy the more it is pulled.

As well as this stretchiness of the lung tissue, *surface tension* makes a key contribution to compliance. All molecules in a liquid are subjected to strong intermolecular attractive forces acting in all directions. Since



**Fig. 43.** Static volume pressure relationships for the lungs and chest wall.

intermolecular interactions in a gas are far weaker than those in a liquid, when a molecule is at a liquid-gas boundary attractive forces acting from below (within the liquid) are much stronger than those acting from above (with the gas). This creates a net force acting perpendicular to the liquid-gas boundary which is called the surface tension. If the boundary is curved, as is the case with alveoli, this surface tension acts towards the centre of the curvature and results in a collapsing force. If an alveolus is to be inflated, these forces must be overcome.

Classically, LaPlace's law has been applied to give a relationship between the radius of an alveolus, the surface tension and the transmural pressure difference needed to counteract this surface tension and prevent the alveolus from collapsing. LaPlace's law is effectively a statement of Newton's Third Law, "for every action there is an equal and opposite reaction". In this case two forces act, an outward force due to the transmural pressure difference across the alveolar wall and an inward force due to the transmural tension in the wall. Both of these forces are expressed per unit length. For a thin-walled sphere:

$$P_i - P_o = \frac{2T}{r}$$

where  $P_i$  = pressure inside the alveolus (Pa **or** mmHg)  
 $P_o$  = pressure outside the alveolus in the intrapleural space  
(Pa **or** mmHg)  
 $T$  = transmural tension in the wall per unit length ( $\text{N}\cdot\text{m}^{-1}$ )  
 $r$  = radius (m).

This is dealt with further in the Appendix. However, application of LaPlace's law requires the implicit assumptions that alveoli are perfectly spherical and are not continuous with each other. Neither of these assumptions are strictly true. Nonetheless, with these caveats in mind, we can still gain useful insights into the importance of surface tension forces by applying LaPlace's law.

Hence for a given surface tension, the transmural pressure difference ( $P_i - P_o$ ) needed to keep an alveolus open is inversely proportional to its radius. It follows that a small alveolus needs a larger transmural pressure difference to keep it open than does a large alveolus. Water has a surface tension of  $0.07 \text{ N}\cdot\text{m}^{-1}$ . Therefore for a small alveolus with a radius of  $50 \mu\text{m}$  filled with water, the transmural pressure gradient,  $P_i - P_o$ , needed to prevent collapse is given by:

$$P_i - P_o = \frac{2 \cdot 0.07}{50 \cdot 10^{-6}} = 2.8 \cdot 10^3 \text{ Pa}$$

and since  $1 \text{ cmH}_2\text{O} \simeq 100 \text{ Pa}$

$$P_i - P_o = 28 \text{ cmH}_2\text{O}$$

At end-expiration, the intra-alveolar pressure is zero. Therefore, to prevent this alveolus from collapsing, the intrapleural pressure, would need to be huge,  $-28 \text{ cmH}_2\text{O}$ . In fact the intrapleural pressure is around  $-5 \text{ cmH}_2\text{O}$  at end-expiration, so *something* must be lowering the surface tension. That something is *surfactant*, a complex mixture of proteins produced by a specialised class of alveolar cells which coats the inner surface of alveoli. Surfactant lowers surface tension to around  $0.012 \text{ N}\cdot\text{m}^{-1}$ . The most important component of surfactant, dipalmitoyl phosphatidyl choline, interposes itself between water molecules in the film covering the inner-alveolar membrane. This disrupts hydrogen bonding and reduces the forces needed to overcome the intermolecular interactions between water molecules. As a result,

the intrapleural pressures needed to keep alveoli open are reduced by a factor of:

$$\frac{0.07}{0.012} = 5.8$$

meaning that the alveolus used in the example will be kept open by intrapleural pressures of  $-4.8 \text{ cmH}_2\text{O}$ . This is a far more realistic value. Another way of putting this is to say that surfactant greatly increases the change in lung volume produced by a given change in intrapleural pressure, i.e. it significantly *increases* lung compliance.

Changes in the arrangement of surfactant molecules with changing volume alters lung compliance. This largely explains the phenomenon of *hysteresis* (the relationship between pressure and volume seen on a static pressure volume curve being different on inspiration and expiration), much beloved of respiratory physiologists. This is certainly a valid phenomenon but only has a noticeable effect at very low lung volumes, well below the normal working range.

#### 4.1.4 Resistance

So far we have ignored the passage of air between the atmosphere (at the mouth) and the alveoli. In fact, the airways provide considerable

##### **Clinical Box 11: Infant Respiratory Distress Syndrome**

One of many problems faced by premature neonates is *Infant Respiratory Distress Syndrome* (IRDS), a disorder resulting from the absence of surfactant leading to decreased lung compliance (this defines a *restrictive lung disease*, see later). IRDS is seen in neonates born before the 32<sup>nd</sup> week of gestation, the point at which fetuses begin to produce surfactant. IRDS can be treated by giving synthetic surfactant to the neonate through a tube inserted into the airways. Endogenous surfactant production is usually triggered by the corticosteroid surge occurring before birth. If time allows, synthetic corticosteroids can be given to the mother before delivery to stimulate surfactant production.

resistance to the flow of air. As for the flow of any fluid along a tube, the resistance along the tube is given by Poiseuille's law (assuming that certain key conditions are met, see Further Thoughts) which tells us that:

$$R_{\text{fluid}} \propto \frac{1}{r^4}$$

where  $R_{\text{fluid}}$  = resistance to fluid flow ( $\text{kg}\cdot\text{m}^{-2}\cdot\text{s}^{-2}$  **or**  $\text{mmHg}\cdot\text{L}^{-1}\text{min}$ )  
 $r$  = radius of pipe (m)

By Darcy's law:

$$\Delta P = \dot{V} \cdot R_{\text{fluid}}$$

where  $\Delta P$  = pressure difference driving flow (Pa **or** mmHg)  
 $\dot{Q}$  = flow along the tube ( $\text{m}^3\cdot\text{s}^{-1}$  **or**  $\text{L}\cdot\text{min}^{-1}$ ),

so if  $R_{\text{fluid}}$  increases, the pressure gradient required to produce the same flow increases.

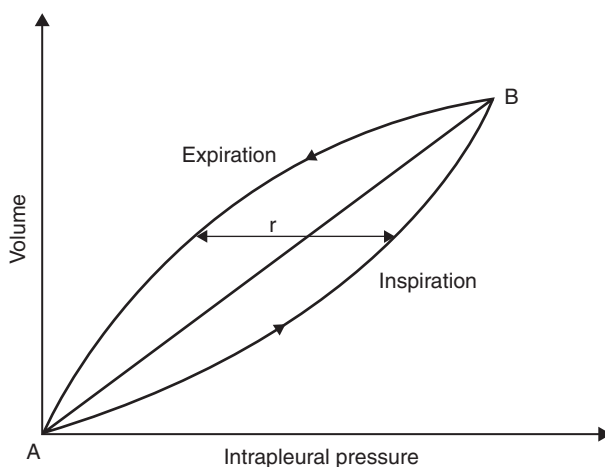
We can use these equations to explain why it is not possible to breathe through a long snorkel and largely why people with asthma have problems breathing. Increasing the length of the resistor through which air must flow, e.g. by breathing through a snorkel, will proportionately increase the resistance and in turn increase the overall pressure gradient needed to produce flow. The maximum intra-alveolar pressure which can be generated even on forced expiration is around 20 cmH<sub>2</sub>O and this imposes an absolute limit on the length of a snorkel through which one can breathe. Similarly, decreasing the radius of the resistor will hugely increase in the overall pressure gradient needed to maintain flow. Asthma, the archetypal example of an *obstructive lung disease*, is characterised by airway narrowing, i.e. decreased airway radius. This can be experienced by breathing through a straw.

Since the airways are tethered to the lung tissue, as lung volume increases during inspiration  $r$  increases and, therefore,  $R_{\text{fluid}}$  decreases, as lung volume increases during inspiration. If we further assume that intra-alveolar pressure is constant during expiration then, it follows from Darcy's law that the highest air flow will be achieved when lung volume is at its highest. Furthermore, air flow will decline during

expiration. A consequence of this is that healthy patients exhale the majority of the air in their lungs in the first second of a forced expiration. A decrease in this proportion is an important marker of the severity of obstructive lung diseases such as asthma which result from increases in  $R_{\text{fluid}}$ .

#### 4.1.5 The energy needed to breathe

While the ultimate purpose of breathing is to provide  $\text{O}_2$  and remove  $\text{CO}_2$  and allow the continued conversion of energy into a useable form, it is important to remember that the act of breathing itself consumes energy. As shown on the next page, the total work done (or energy converted) during a respiratory cycle is given by the area enclosed within a *dynamic volume pressure loop* obtained during normal breathing (Fig. 44). Notably, the gradient of the line AB on such a curve gives the mean compliance over the respiratory cycle, while the length of the line  $r$  gives an index of the airway resistance. This includes both work done in stretching the lungs and chest wall, which depends entirely on compliance, and work done in moving air through the airways, which depends on resistance. We see this in



**Fig. 44.** Dynamic volume pressure loop obtained during breathing.

### The Energy Needed to Breathe

To understand why the total work done during a respiratory cycle is given by the area enclosed by the dynamic volume pressure loop we will begin by thinking about the work done during inspiration:

$$E = \int F dx$$

Now

$$F = \int PdA$$

so

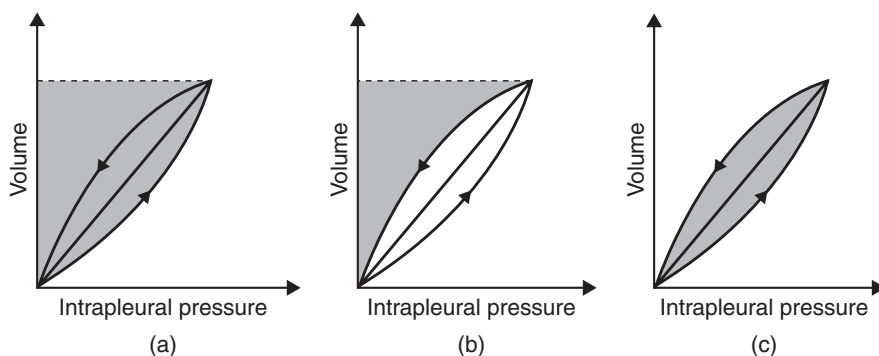
$$E = \int \left( \int PdA \right) dx$$

and since

$$V = \int PdA$$

we have  $E = \int PdV$ , i.e. the area between the inspiratory volume-pressure curve and the y-axis in Fig. 45.

By the same argument, the elastic energy released during expiration is given by the area between the expiratory volume-pressure curve and the y-axis (area b). Much of the energy consumed during inspiration in doing elastic work is returned during expiration but clearly areas a and b are not equal: some energy must have been lost, i.e. net work must have been done. Most of the energy consumed as we breathe is used in doing work against the airway resistance (airway resistive work) and this accounts for most of area c. This is tantamount to saying that these loops also show a sort of *hysteresis* due to airways resistance. Incidentally, a little energy is also consumed doing work against frictional forces acting between tissues moving against each other (*tissue resistive work*): as mentioned earlier, this resistance is minimised by the presence of lubricating fluid in the intrapleural space.

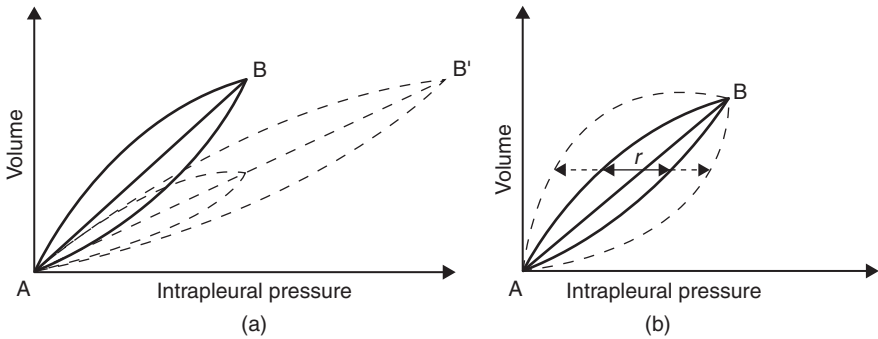


**Fig. 45.** Volume pressure loops.

### **Clinical Box 12: Restrictive and Obstructive Lung Diseases**

In restrictive lung diseases such as *pulmonary fibrosis*, the average compliance of the lungs or chest wall during inspiration and expiration is decreased. This is illustrated in the volume-pressure loops shown in Fig. 46. For simplicity, these consider the lung tissue only and do not show hysteresis. Decreased average compliance is reflected in a decrease in the slope of the line AB. It follows that more work must then be done to cause air to flow into the lungs, either by achieving the same volume in each breath (by increasing the magnitude of the negative intrapleural pressure on inspiration and hence the area of the loop) or by increasing the number of breaths per unit time (by increasing the respiratory rate). Both these possibilities result in an increase in the work done per unit time (power output).

In obstructive lung diseases such as asthma, the resistance of the airways is increased, resulting in an increase in the horizontal width of the loop,  $r$ . In order to cause air to flow into the lungs the area of the loop must again be increased, representing an increase in the work done.



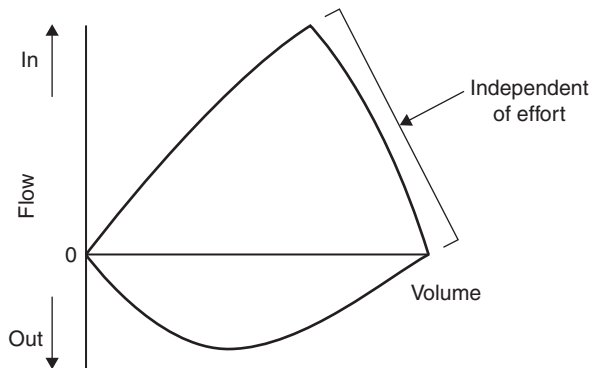
**Fig. 46.** Volume pressure loops in restrictive and obstructive lung diseases (dotted lines).

Clinical Box 12 where we consider the *restrictive* and *obstructive lung diseases*, clinical situations in which these factors change.

Ordinarily, the energy required for respiration represents something between 2% and 5% of the body's total energy consumption. Since at steady state our metabolism must be entirely aerobic this means that breathing accounts for 2% to 5% of  $O_2$  consumption. In severe restrictive or obstructive lung disease, this may increase to 20% or more. Very sick patients may find themselves in an unwinnable positive-feedback cycle where  $O_2$  is made available to the body at an insufficient rate, but increasing the depth or rate of breathing only serves to worsen the problem.

#### 4.1.6 Elastic recoil and expiratory flow

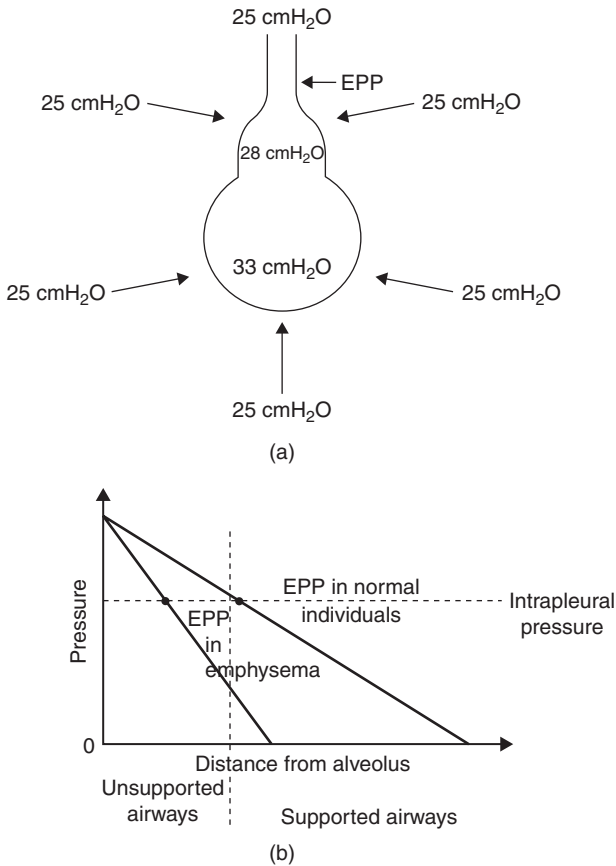
A great deal of physiologically and clinically important information can be gathered by analysing relationships between air flow and lung volume. Such a curve plotted in a healthy patient is shown in Fig. 47. Flow reaches a peak soon after expiration begins and then just as quickly begins to decline. While the ascending portion of the curve is affected by effort, the descending portion of the curve is not. This reveals an interesting and clinically important property of the airways. It is the *longitudinal* pressure difference between the alveoli and the atmosphere that results in air flow out of the lungs during



**Fig. 47.** Flow volume loop.

expiration. However, it is the *transverse* pressure difference between the alveoli and the intrapleural space that results in the airways remaining open.

During forced expiration, the intrapleural pressure increases and becomes positive and therefore the intra-alveolar pressure also increases. An added contribution from the elastic recoil of the lung in fact elevates the intra-alveolar pressure above the intrapleural pressure: the transverse pressure difference between the intra-alveolar space and the intrapleural space is therefore positive. It is this positive pressure difference that keeps the airways open. As we move along the airways towards the mouth, the intra-airway pressure progressively falls because of airway resistance. At some point along the airways, intra-airway pressure will equal intrapleural pressure which is constant throughout the intrapleural space: this is known as the *equal-pressure point* (EPP). On quiet expiration, the EPP is located in the main bronchi which have the benefit of cartilaginous support to hold them open. However, on forced expiration, the EPP moves towards the lungs. If the EPP is reached in the airways distal to the terminal bronchioles, which lack support from cartilage, the airways will collapse and expiratory flow will be limited. Importantly, this means that it is the elastic recoil of the lung, determined by its compliance, that in fact determines maximum expiratory flow. Furthermore, expiratory flow cannot be increased by increasing effort. This is because increasing



**Fig. 48.** Airway compression and the equal pressure point.

effort increases intrapleural pressure and an increase in intrapleural pressure will also proportionately increase the intra-alveolar pressure, thus having no effect on the EPP. This is illustrated in Fig. 48.

## 4.2 The Exchange of Gases Between the Lungs and the Blood

Having considered the process of moving O<sub>2</sub> and CO<sub>2</sub> between the atmosphere and the alveoli, we are now in a position to consider how these gases are exchanged between the alveoli and the blood. Naturally both these processes occur down an energy gradient. While

**Clinical Box 13: Chronic Obstructive Pulmonary Disease (COPD)**

The mechanical changes underlying COPD are somewhat more complex and interesting. COPD has two components: chronic bronchitis (clinically defined as a cough producing sputum for at least three months of the year for at least two consecutive years), which contributes an obstructive component, and emphysema (abnormal permanent dilatation of air airways distal to the terminal bronchioles). In emphysema, damage to the alveolar walls results in increased lung compliance. This is clearly not a problem during inspiration. However, it means that less elastic potential energy is then stored to be released on expiration. This leads to elastic recoil making a smaller-than-usual contribution to the intra-alveolar pressure. The transverse pressure gradient between the airways and the intrapleural spaces decreases, moving the EPP towards the lungs and causing the airways to collapse on expiration. This explains why patients with emphysema find some relief by breathing through pursed lips: breathing through a narrow tube increases airway resistance, decreasing flow and, as a consequence of Darcy's law, increasing the intra-airway pressure. This moves the EPP towards the mouth, hopefully to parts of the airways which are held open with cartilage and are therefore non-collapsible. The same reasoning explains why babies with IRDS grunt: without surfactant, alveolar surface tension is high, tending to make them collapse on expiration. Narrowing the vocal cords increases the resistance of the larynx and increases the intra-airway pressure. This moves the EPP upwards and helps to prevent the alveoli from collapsing.

a pressure gradient drives exchange between the atmosphere and the alveoli, a concentration gradient drives exchange between the alveoli and blood. Here, a concentration difference, rather than pressure difference, is key as gases are dissolved in solution as they enter the blood. However, pressures, or more specifically partial pressures, are still important as they in turn determine the concentration of a gas in

solution. Here:

$$P_p = \text{fraction of gas mixture} \cdot \text{total pressure}$$

where  $P_p$  = partial pressure (Pa **or** mmHg). Hence

$$C = P_p \cdot S$$

where  $C$  = concentration ( $\text{mol} \cdot \text{m}^{-3}$  **or**  $\text{mol} \cdot \text{L}^{-1}$ )

$S$  = solubility in blood at body temperature ( $(\text{m}^3) \cdot \text{m}^{-2} \cdot \text{kg} \cdot \text{s}^{-2}$   
**or**  $\text{ml} \cdot \text{L}^{-1} \cdot \text{mmHg}^{-1}$ ).

As with any flow, the *rate* at which this transfer occurs depends not only on this energy difference but also on the resistance to flow. Fick's law states that

$$j = \frac{A}{d} \cdot D \cdot S \cdot \Delta P_p$$

where  $j$  = rate of diffusion ( $\text{m} \cdot \text{s}^{-1}$ )

$A$  = area ( $\text{m}^2$ )

$d$  = distance over which diffusion occurs (m)

$D$  = constant of proportionality related to the diffusion  
co-efficient ( $\text{m} \cdot (\text{m}^{-3}) \cdot \text{s}^3 \cdot \text{kg}^{-2}$  **or**  $\text{L} \cdot (\text{ml})^{-1} \cdot \text{s}^{-1}$ )

$\Delta P_p$  = partial pressure difference (Pa **or** mmHg)

From this, we can see that the flow of gas between the lungs and the blood will depend on:

- (1) the surface area of the alveoli over which exchange can occur ( $A$ );
- (2) the combined distance across the alveolar membrane, the interstitial space and the capillary membrane ( $d$ );
- (3) the diffusion coefficient for the gas (related to  $D$ );
- (4) the solubility of each gas in blood ( $S$ );
- (5) the difference in partial pressure between the alveoli and the blood for each gas ( $\Delta P_p$ ).

The first two factors apply equally to any gas while the final three are specific to a particular gas.

- *Surface area (A)*

The alveolar surface area is significantly larger than that of any other membrane in the body, averaging 75 m<sup>2</sup> (the area of a tennis court) in an adult man. Not all this area normally receives ventilation and perfusion, however. Increases in blood supply and ventilation as occur during exercise can therefore increase the area used and thus the rate of diffusion.

- *Diffusion distance (d)*

Despite the several layers separating alveolar gas and blood, diffusion distance is ordinarily small (around 0.3 μm). However, this may be increased if the alveolar membrane is thickened as in pulmonary fibrosis, or if fluid accumulates in the alveoli as in pulmonary oedema or pneumonia.

- *Diffusion coefficient (D)*

The diffusion coefficient for a gas is related to its molecular weight:

$$D \propto \frac{1}{\sqrt{MW}}$$

Since

$$\sqrt{\frac{MW_{CO_2}}{MW_{O_2}}} = \sqrt{\frac{32}{44}} = \sqrt{0.73} = 0.85$$

all other factors being equal, CO<sub>2</sub> should diffuse at 0.85 times the rate at which O<sub>2</sub> diffuses. However, this is massively offset by CO<sub>2</sub> being so much more soluble in water than O<sub>2</sub> as we will see below.

- *Solubility of each gas in blood (S)*

The major constituents of atmospheric gas are nitrogen, oxygen and carbon dioxide. Nitrogen constitutes 78% of atmospheric gas but we can largely ignore it here as it is not used by the body and therefore no concentration gradient exists for its exchange. This itself illustrates an important principle: it is only because the body consumes O<sub>2</sub> and produces CO<sub>2</sub> that concentration gradients exist for these gases. If it

were possible to temporarily stop cells from respiring, O<sub>2</sub> and CO<sub>2</sub> exchange would cease.

Importantly, the solubilities of these gases in blood, or to a first approximation in water, differ significantly:

$$S_{\text{O}_2} = 0.03 \cdot \text{ml} \cdot \text{L}^{-1} \cdot \text{mmHg}^{-1}$$

$$S_{\text{CO}_2} = 0.69 \cdot \text{ml} \cdot \text{L}^{-1} \cdot \text{mmHg}^{-1}$$

Therefore, at the same partial pressure, the concentration of CO<sub>2</sub> will be 23 times that of O<sub>2</sub>. All other factors being equal, CO<sub>2</sub> should diffuse 23 times faster than O<sub>2</sub>. This is partially offset by differences in the diffusion coefficient, but  $0.85 \times 23$  still leaves us with CO<sub>2</sub> diffusing 20 times faster than O<sub>2</sub>. Under normal conditions this is not of great importance as there is sufficient time available for diffusion of both gases to occur. However, if diffusion is compromised for any other reason, perhaps because mucus and secretions increase the thickness of the diffusion barrier as in pneumonia, the transfer of O<sub>2</sub> is affected more rapidly and to a much greater degree than that of CO<sub>2</sub>. This can result in a decrease in  $P_{\text{aO}_2}$  without a concomitant increase in  $P_{\text{aCO}_2}$ . Such *hypoxia* (defined as a  $P_{\text{aO}_2}$  of less than 60 mmHg) without *hypercapnia* (defined as a  $P_{\text{aCO}_2}$  of greater than 45 mmHg) is termed Type 1 respiratory failure. As a brief aside, hypoxia with hypercapnia is termed Type 2 respiratory failure. This usually results from mechanical disorders.

- *Partial pressure difference* ( $\Delta P_p$ )

Since the solubility of a given gas in blood is effectively constant, it is changes in partial pressure that are key to determining changes in the concentration of gas dissolved in blood. Given that the surface area over which diffusion can occur is so large and that sufficient time is usually available for diffusion, it would not be unreasonable to expect that equilibrium should be reached and arterial partial pressures should be equal to alveolar partial pressure, i.e.  $P_{\text{aO}_2} = P_{\text{AO}_2}$ . In fact, this does not quite happen: even in healthy patients  $P_{\text{aO}_2}$  (circa 95 mmHg) is always less than  $P_{\text{AO}_2}$  (circa 100 mmHg). The reasons for this are worth some attention.

### 4.2.1 Ventilation and perfusion

There are two main reasons for this difference. The first is venous to arterial *shunting*. This describes the mixing of systemic venous blood that has not passed through the pulmonary circulation with systemic arterial blood. Such shunts may be either *anatomical* or *functional* (physiological).

In healthy subjects, there are two main causes of *anatomical* shunting: some coronary venous blood drains into the left ventricle via the Thebesian veins and some blood from the bronchial circulation drains into the pulmonary veins. Combined, these normally constitute less than 2% of the cardiac output. However, this can increase significantly when structural abnormalities of the heart cause blood to pass from its right side (deoxygenated) directly to its left side (oxygenated). This type of shunting can be identified clinically by the fact that breathing  $O_2$  at an increased partial pressure does not improve  $P_{aO_2}$ .

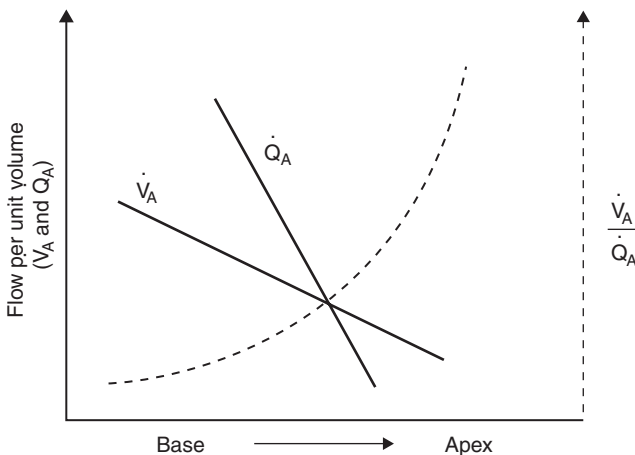
*Functional* shunting also occurs in healthy patients. This is seen when alveoli are not ventilated but are still perfused, perhaps as a result of collapse or blockage with mucus. This leads us to the other cause of the difference between arterial and alveolar partial pressures. When standing upright the weight of the lungs tends to pull them towards to the chest wall to a greater degree at the base than at the apex. This results in the intrapleural pressure at the end of expiration being less negative at the base ( $-2.5 \text{ cmH}_2\text{O}$ ) than at the apex ( $-10 \text{ cmH}_2\text{O}$ ). The alveoli at the base of the lung are, therefore, not as expanded as those at the apex. Since lung compliance increases as volume decreases (see Fig. 44), the base has a higher compliance than the apex. The circa  $3 \text{ cmH}_2\text{O}$  change in intrapleural pressure that occurs on inspiration will therefore lead to a greater change in volume at the base than at the apex, meaning that the base will be better ventilated. In fact when standing upright, the alveoli at the base of the lungs receive around 2.5 times as much ventilation per unit volume than alveoli at the apex. Notably the effect of such functional shunting on  $P_{aO_2}$  can be offset by breathing  $O_2$  at an increased partial pressure.

As well as affecting alveolar ventilation, gravity also has marked effects on alveolar perfusion. While it has no influence on the

extravascular (intra-alveolar) pressure it is important in determining the intravascular (hydrostatic) pressure. When standing upright, the base of the lung is around 10 cm below the tricuspid valve where blood leaves the heart. Assuming that the density of blood is the same as that of water, this means that the intravascular pressure will be increased by 10 cmH<sub>2</sub>O and this will in turn increase perfusion. By contrast, the apex is around 15 cmH<sub>2</sub>O above the tricuspid valve and so the intravascular pressure there will be decreased by 15 cmH<sub>2</sub>O, decreasing perfusion. In fact, when standing upright alveoli at the base of the lungs receive around six times as much perfusion per unit volume as alveoli at the apex.

Despite both ventilation and perfusion being greater at the base than at the apex, the relative magnitudes of their values and the rates of decrease on moving up the lungs differ. This means that the ventilation to perfusion ratio ( $\dot{V}_A : \dot{Q}_A$ ) varies throughout the lung (Fig. 49).

Let us imagine what would happen with extreme values of  $\dot{V}_A : \dot{Q}_A$ . If an alveolus is unventilated but well perfused, the partial pressures of gases in the blood leaving it will remain the same as those in the mixed-venous blood perfusing it. If on the other hand, an alveolus is well ventilated but completely unperfused, the partial pressures of gases in the alveolus will remain the same as in the inspired air as none of the oxygen will be able to enter the blood. Of course these extremes



**Fig. 49.** Ventilation: perfusion relationships.

are not normally reached but they illustrate the principle at work. In a healthy lung,  $V_A : Q_A$  is around 0.6 at the base while at the apex it is around 3. Interestingly *Mycobacteria*, which cause tuberculosis, grow best where  $P_{O_2}$  is high. This might explain why the apices are often affected first in pulmonary tuberculosis. For the lung as a whole,  $V_A$  is typically  $5 \text{ L}\cdot\text{min}^{-1}$  while  $Q_A$  is typically  $6 \text{ L}\cdot\text{min}^{-1}$ , giving an average  $V_A : Q_A$  for the entire lung of 0.8. This results in an average  $P_{AO_2}$  of 100 mmHg and  $P_{ACO_2}$  of 40 mmHg. Since both  $V_A$  and  $Q_A$  are greater at the base than at the apex, the base makes a proportionally greater contribution to both the mix of expired gas and arterial partial pressures.

### 4.3 The Carriage of Gases in the Blood

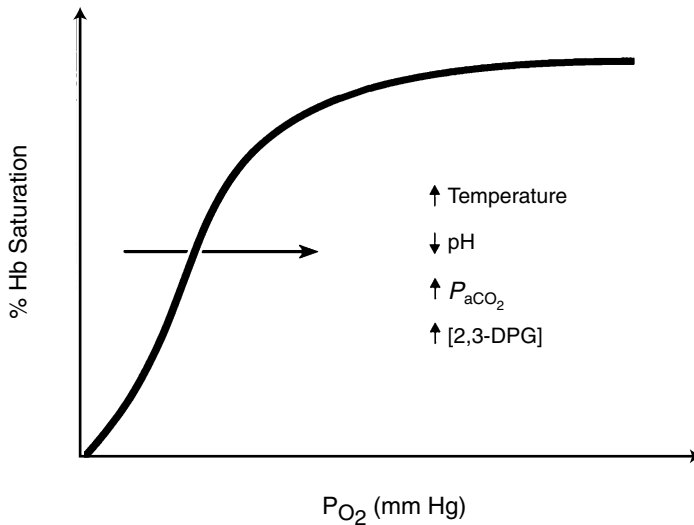
Having considered how gases are transported into and out of the lungs and transferred to the blood, we now need to think about how they are carried in the blood. Given that 0.03 ml of  $O_2$  dissolves in each litre of blood for each mmHg pressure, at a  $P_{AO_2}$  of 100 mmHg each litre of blood contains 3 ml of  $O_2$ . The body's resting  $O_2$  consumption is around  $300 \text{ ml}\cdot\text{min}^{-1}$  so if  $O_2$  were exclusively carried dissolved in solution a cardiac output of  $100 \text{ L}\cdot\text{min}^{-1}$  would be needed. Clearly, this is wildly unrealistic so some other means of transporting  $O_2$  is absolutely essential. Up to 98.5% of  $O_2$  in blood is carried bound to haemoglobin (Hb) molecules inside red blood cells. Binding to this protein increases the total  $O_2$  content of each litre of blood to around 200 ml, compatible with a far more reasonable cardiac output. Happily, while Hb dramatically increases the  $O_2$ -carrying capacity of the blood, the binding of  $O_2$  to Hb has no effect on either the concentration of  $O_2$  dissolved or on the  $P_{aO_2}$  so everything said above still holds true.

We need not concern ourselves here with the biochemistry of the Hb molecule but we should think a little about its properties.

The total amount of  $O_2$  bound to Hb per unit volume of blood must depend on the number of Hb molecules per unit volume of blood, the ability of these molecules to bind  $O_2$  (their *affinity*) and the proportion of Hb molecules that have bound  $O_2$  (are saturated with  $O_2$ ).

It is intuitive that the more Hb molecules per unit volume of blood, the greater the  $O_2$  content will be. Conversely, if the number of Hb molecules per unit volume of blood decreases, the capacity for  $O_2$  carriage will decrease. Decreases in the Hb content of the blood or in the ability of Hb to bind  $O_2$  occur in *anaemia*. Since in either case, there is in effect less useful Hb available, the total  $O_2$  content of blood at any given  $P_{aO_2}$  will be decreased. If the circulatory system is to continue to deliver the same quantity of  $O_2$  per unit time to the tissues, then the cardiac output must increase. This explains why anaemia is particularly associated with an increase in heart rate.

The proportion of these Hb molecules saturated with  $O_2$  depends on the  $P_{aO_2}$ . This relationship is described by the  $O_2$ -Hb dissociation curve (which could just as well be called an *association* curve) (Fig. 50). The characteristic sigmoidal shape of this curve results from each Hb molecule being able to bind four  $O_2$  molecules in a *cooperative* manner so that the affinity of Hb for  $O_2$  increases as each of four  $O_2$  molecule binds. The curve is flat over the normal working range of  $P_{AO_2}$  values, meaning that blood still becomes almost fully saturated

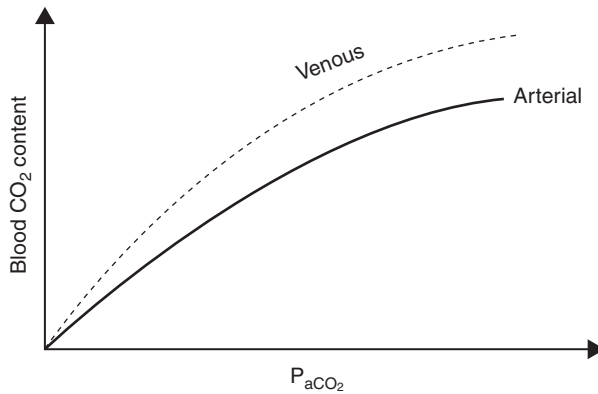


**Fig. 50.**  $O_2$ -haemoglobin dissociation curve.

with  $O_2$  as it passes through the lungs. Notably,  $P_{aO_2}$  values as low as 50 mmHg have been reported in healthy subjects during a long haul flight. Nevertheless, this is usually still on the flat part of the curve and therefore Hb saturation may still be greater than 90%. As helpful as this seems, it also means that manoeuvres such as hyperventilation or breathing  $O_2$  at a high partial pressure do not significantly increase the  $O_2$  content of the blood in a healthy person. This also necessitates caution when interpreting *pulse oximeter* readings. These give a simple clinical indication of a patient's Hb saturation. While such readings are useful in identifying when  $P_{aO_2}$  is very low, they do not reflect mild or moderate decreases in  $P_{aO_2}$  as large decreases are needed before Hb saturation starts to fall.

The shallow slope of the  $O_2$ -Hb dissociation curve over the values of  $P_{O_2}$  encountered in the lungs limits the effects of small changes in  $P_{aO_2}$  on the  $O_2$  content of the blood. In contrast, its steep slope over the values of  $P_{aO_2}$  normally seen at the tissues allows Hb to give up its bound  $O_2$ . What is more, a small decrease in tissue  $P_{aO_2}$  results in a significant decrease in Hb saturation, i.e. increases unloading. More active tissues with lower  $P_{aO_2}$  values will therefore receive more  $O_2$  than resting tissues with higher  $P_{aO_2}$ s. Active tissues also produce more  $CO_2$  and  $H^+$ . Both of these decrease the affinity of the Hb for  $O_2$ , shifting the dissociation curve to the right (see Fig. 50) and further facilitate  $O_2$  unloading. This is referred to as the *Bohr effect*. In addition, the rate of production of 2,3-diphosphoglycerate (2,3-DPG, a sugar) increases as the rate of glycolysis increases. This acts directly on the Hb molecule to decrease  $O_2$  affinity and further shift the curve to the right. Together, these effects mean that the amount of  $O_2$  unloaded in the tissues is primarily dependent on the activity, and therefore demand, of the tissues.

In contrast to  $O_2$ ,  $CO_2$  is readily soluble in water. While less than 1.5% of  $O_2$  carried in blood is dissolved in solution, up to 6% of the total  $CO_2$  content of blood is represented by dissolved gas. Of the remaining 94%, around 5% is carried as carbamino compounds, formed when  $CO_2$  binds to amine groups on plasma proteins and Hb. The most important form in which  $CO_2$  is carried, however, is  $HCO_3^-$ . When dissolved in plasma  $CO_2$  reacts with water to form carbonic

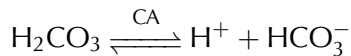


**Fig. 51.** Relationship between  $P_{aCO_2}$  and blood  $CO_2$  content.

acid:

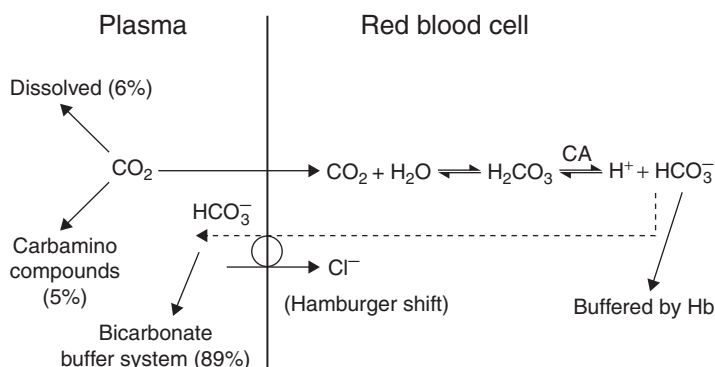


As  $H_2CO_3$  is a weak acid, it does not significantly dissociate. However, it is able to diffuse into red blood cells and these contain a vital enzyme, *carbonic anhydrase* (CA) which dramatically increases the rate at which carbonic acid dissociates:



$H^+$  can then be buffered inside the red blood cell. As explained above, as Hb binds  $H^+$ , its affinity for  $O_2$  falls (the *Bohr effect*), encouraging Hb to give up  $O_2$  at the tissues where the  $P_{CO_2}$  is high. The counterpoint is also true: the affinity of Hb for  $H^+$  is increased as  $O_2$  unloads (the *Haldane effect*). The relationship between blood  $CO_2$  content and  $P_{aCO_2}$  is shown in Fig. 51.

$HCO_3^-$  is exchanged across the cell membrane for  $Cl^-$  (the chloride shift or *Hamburger phenomenon*). This maintains the intracellular charge, and hence the potential difference across the cell membrane, while allowing  $HCO_3^-$  to enter the plasma and perform its vital function as a buffer (see later). This in turn results in net accumulation of  $Cl^-$  which this leads to an osmotic gradient for water entry into the red blood cell. Increased red blood cell volume as a result of  $CO_2$ -loading explains why the proportion of the blood volume accounted for by



**Fig. 52.** Summary of CO<sub>2</sub> handling.

red blood cells (the packed red cell volume) is some 3% larger in the systemic veins as compared to the arteries! These processes are summarised in Fig. 52.

## FURTHER THOUGHTS

### 4.4 The Alveolar Gas Equation

It is clear that the delivery of O<sub>2</sub> to the tissues is ultimately dependent on maintaining a sufficient partial pressure of O<sub>2</sub> in the alveoli. With a few assumptions, we can derive a simple equation describing the key factors determining the partial pressure exerted by O<sub>2</sub> in the alveoli. We will go on to make the assumption throughout that the partial pressures of gases in the alveoli are approximately equal to those in the arterial blood ( $P_{aO_2}$ ). The same applies for CO<sub>2</sub>. We will begin by considering the inputs and outputs of gases to and from the alveoli.

O<sub>2</sub> enters the alveoli from the atmosphere at a rate which depends on the volume of gas entering the alveoli per unit time, the alveolar ventilation rate.

$$\text{input} = \dot{V}_A \cdot F_{IO_2}$$

where input = rate of input of  $O_2$  to alveoli ( $m^3 \cdot s^{-1}$  **or**  $L \cdot \text{min}^{-1}$ )

$V_A$  = alveolar ventilation rate ( $m^3 \cdot s^{-1}$  **or**  $L \cdot \text{min}^{-1}$ )

$F_{IO_2}$  = fraction of inspired gas represented by  $O_2$   
(dimensionless)

$O_2$  leaves the blood in two directions:

- across the alveolar membrane into the blood (which at steady state represents the rate of  $O_2$  consumption).
- back to the atmosphere in expired gas.

The first of these is simply given by the rate of  $O_2$  consumption. The second is given by  $V_A \cdot F_{AO_2}$ :

$$\text{output} = \dot{V}_{O_2} + \dot{V}_A \cdot F_{AO_2}$$

where output = rate of output of  $O_2$  from alveoli ( $m^3 \cdot s^{-1}$  **or**  $L \cdot \text{min}^{-1}$ )

$F_{AO_2}$  = fraction of alveolar gas represented by  $O_2$   
(dimensionless)

If the  $P_{AO_2}$  is constant, then the rate at which  $O_2$  is being added to the alveoli (input) must be equal to the rate at which it is removed (output). Therefore:

$$\dot{V}_A \cdot F_{IO_2} = \dot{V}_{O_2} + \dot{V}_A \cdot F_{AO_2}$$

rearranging

$$\dot{V}_{O_2} = \dot{V}_A (F_{IO_2} - F_{AO_2})$$

#### **4.4.1 Factors determining $P_{AO_2}$**

If we assume that the alveolar pressure is equal to the atmospheric pressure and that the air is dry, then by Dalton's law:

$$F_{O_2} = \frac{P_{O_2}}{P_{\text{atmos}}}$$

where  $F_{O_2}$  = fraction of gas represented by  $O_2$  (dimensionless)

$P_{O_2}$  = partial pressure of  $O_2$  (Pa **or** mmHg)

$P_{atmos}$  = atmospheric pressure (Pa **or** mmHg)

so

$$\dot{V}_{O_2} = \dot{V}_A \left( \frac{P_{IO_2} - P_{AO_2}}{P_{atmos}} \right),$$

where  $P_{IO_2}$  = partial pressure of  $O_2$  in inspired gas (Pa **or** mmHg)

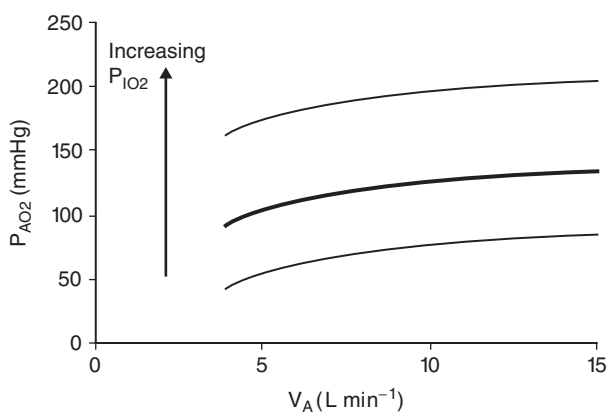
$P_{AO_2}$  = partial pressure of  $O_2$  in alveolar gas (Pa **or** mmHg)

which rearranges to:

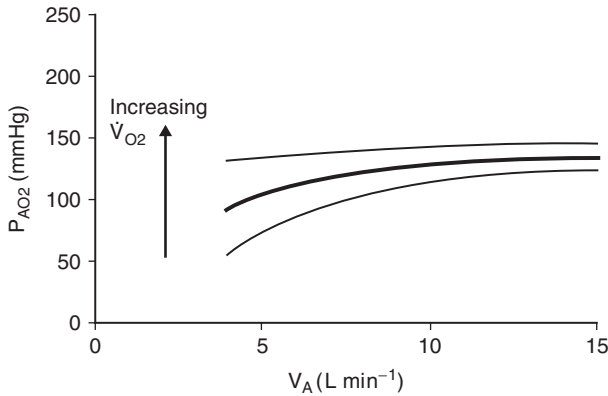
$$P_{AO_2} = P_{IO_2} - \frac{V_{O_2} \cdot P_{atmos}}{\dot{V}_A}.$$

This allows us to examine graphically the effect of each parameter on  $P_{AO_2}$ . To keep things simple, we plot  $P_{AO_2}$  against  $V_A$ , changing each of the other parameters one at a time (Figs. 53 and 54).

For each of the family of hyperbolae,  $P_{AO_2}$  can be increased by increasing  $V_A$ , i.e. by hyperventilating, and decreased by decreasing  $V_A$ , i.e. by hypoventilating. From the equation, increasing  $P_{IO_2}$  shifts the curve upwards (Fig. 53, arrow), while decreasing  $P_{IO_2}$  shifts the curve downwards. In a mechanically ventilated patient, it would be



**Fig. 53.** The effect of increasing  $P_{IO_2}$  on the relationship between  $P_{AO_2}$  and  $V_A$ .



**Fig. 54.** The effect of decreasing  $V_{O_2}$  on the relationship between  $P_{AO_2}$  and  $V_A$ .

possible to alter  $P_{atmos}$  while keeping  $P_{IO_2}$  and  $V_A$  constant, but in reality, this situation never arises. As can be seen from the equation, increasing  $P_{atmos}$  would be expected to shift the curve downwards, while decreasing  $P_{atmos}$  would be expected to shift it upwards. Importantly, at high altitudes both  $P_{IO_2}$  and  $P_{atmos}$  are decreased ( $F_{IO_2}$  is constant). The combined effect of these changes is to shift the curve relating  $P_{AO_2}$  to  $V_A$  downwards, necessitating an increased  $V_A$  to maintain the  $P_{AO_2}$ .

Increasing  $V_{O_2}$  while holding  $P_{IO_2}$  and  $P_{atmos}$  constant (Fig. 54, arrow) shifts the curve downwards while decreasing  $V_{O_2}$  shifts it upwards. Keeping  $P_{atmos}$  and  $V_{O_2}$  fixed at their normal values (760 mmHg and  $300 \text{ ml min}^{-1}$  respectively) and increasing  $P_{IO_2}$ , perhaps by breathing oxygen through a face mask, again shifts the curve upwards, resulting in a large increase in  $P_{AO_2}$  for all values of  $V_A$ .

It is intuitive that  $P_{AO_2}$  can be increased by increasing  $V_A$  but as we see from the equation, it is far more effective to increase  $P_{IO_2}$  while keeping  $P_{atmos}$  constant, i.e. increasing  $F_{IO_2}$ . This is effectively achieved by breathing  $O_2$  from a face mask. However, this option is not usually available in everyday life. Therefore, when faced with an increased  $O_2$  demand, increasing respiratory rate and volume is the most effective option available.  $P_{AO_2}$  can also be increased by

decreasing  $V_{O_2}$ . Of course  $P_{AO_2}$  could also be increased by decreasing  $P_{atmos}$  while keeping  $P_{IO_2}$  constant, again increasing  $F_{IO_2}$ , but this situation seldom exists.

#### 4.4.2 Factors determining $P_{ACO_2}$

Now let us consider  $CO_2$ . Assuming that the tissues do not accumulate  $CO_2$ , it must enter the circulation at the rate at which it is produced by the tissues (around  $200 \text{ ml} \cdot \text{min}^{-1}$ ). Let us assume that all  $CO_2$  produced is immediately delivered to the alveoli, i.e. diffusion across the alveolar capillary membranes occurs completely and instantaneously.

$$\text{input} = \dot{V}_{CO_2}$$

where input = rate at input of  $CO_2$  to alveoli ( $\text{m}^3 \cdot \text{s}^{-1}$  **or**  $\text{L} \cdot \text{min}^{-1}$ )  
 $\dot{V}_{CO_2}$  = rate of  $CO_2$  production ( $\text{m}^3 \cdot \text{s}^{-1}$  **or**  $\text{L} \cdot \text{min}^{-1}$ )

$CO_2$  leaves the alveoli for the atmosphere at a rate dependent on alveolar ventilation:

$$\text{output} = \dot{V}_A \cdot F_{ACO_2}$$

where output = rate of output of  $O_2$  from alveoli ( $\text{m}^3 \cdot \text{s}^{-1}$  **or**  $\text{L} \cdot \text{min}^{-1}$ )  
 $F_{ACO_2}$  = fraction of alveolar gas represented by  $CO_2$   
 (dimensionless)

If  $P_{ACO_2}$  is constant then  $\dot{V}_{CO_2}$  (input) must be equal to the rate at which it is being removed (output). Therefore:

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

By Dalton's law:

$$F_{ACO_2} = \frac{P_{ACO_2}}{P_{atmos}}$$

where  $P_{ACO_2}$  = partial pressure of  $CO_2$  in alveolar gas (Pa **or** mmHg).

So:

$$\dot{V}_{\text{CO}_2} = \frac{P_{\text{ACO}_2}}{P_{\text{atmos}}} \cdot \dot{V}_A$$

and this rearranges to

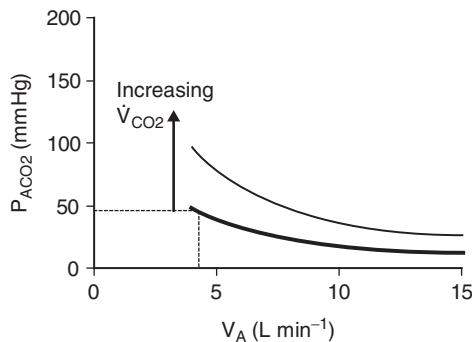
$$P_{\text{ACO}_2} = \frac{\dot{V}_{\text{CO}_2} \cdot P_{\text{atmos}}}{\dot{V}_A}$$

and allows us to plot a family of curves this time relating  $P_{\text{ACO}_2}$  to  $V_A$  for different values of  $V_{\text{CO}_2}$  (Fig. 55). By inspection,  $P_{\text{ACO}_2}$  is inversely proportional to  $V_A$  and so have formally shown that the more we breathe, the more  $\text{CO}_2$  we expire and the lower the  $P_{\text{ACO}_2}$ . Since  $P_{\text{ACO}_2}$  is the key factor determining  $V_A$  (providing our drive to breathe), this constitutes a hugely important example of negative feedback.

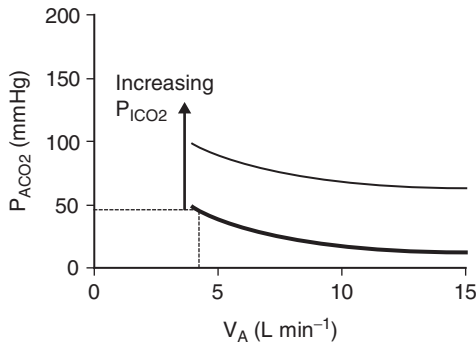
Of course, this assumes that the inspired air contains no  $\text{CO}_2$ . This is usually a fair assumption: in atmospheric gas  $P_{\text{CO}_2}$  is 0.21 mmHg, i.e. negligible. However, if a subject breathes a gas mixture containing a significant  $P_{\text{CO}_2}$  then the expression becomes:

$$P_{\text{ACO}_2} = \frac{V_{\text{CO}_2} \cdot P_{\text{atmos}}}{\dot{V}_A} + P_{\text{ICO}_2}$$

where  $P_{\text{ICO}_2}$  = partial pressure of  $\text{CO}_2$  in inspired gas (Pa **or** mmHg) and this shifts the curve upwards along the y-axis (Fig. 56).



**Fig. 55.** The effect of increasing  $V_{\text{CO}_2}$  on the relationship between  $P_{\text{ACO}_2}$  and  $V_A$  (dotted lines indicate normal values).



**Fig. 56.** The effect of increasing  $P_{I\text{CO}_2}$  on the relationship between  $P_{A\text{CO}_2}$  and  $V_A$  (dotted lines indicate normal values).

#### 4.4.3 The alveolar gas equation

We can now think about combining these two equations. Taking a step aside, the respiratory quotient is defined as:

$$R = \frac{\dot{V}_{\text{CO}_2}}{\dot{V}_{\text{O}_2}}$$

where  $R$  = respiratory quotient (dimensionless).

So

$$R = \frac{\dot{V}_A \cdot F_{A\text{CO}_2}}{\dot{V}_A (F_{I\text{O}_2} - F_{A\text{O}_2})}$$

which simplifies to

$$R = \frac{F_{A\text{CO}_2}}{F_{I\text{O}_2} - F_{A\text{O}_2}}$$

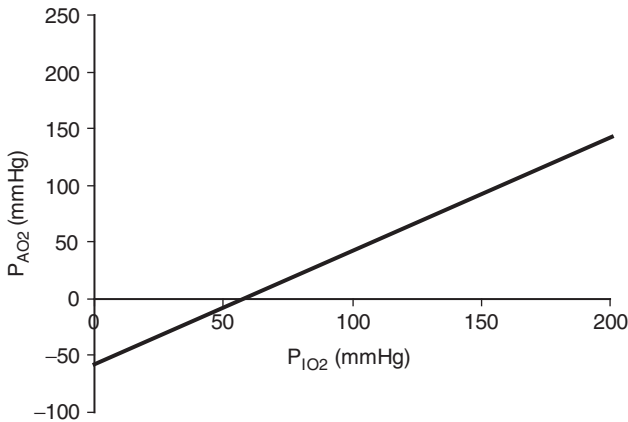
and rearranges to

$$F_{A\text{O}_2} = F_{I\text{O}_2} - \frac{F_{A\text{CO}_2}}{R}$$

or incorporating Dalton's law

$$P_{A\text{O}_2} = P_{I\text{O}_2} - \frac{P_{A\text{CO}_2}}{R}$$

both of which are forms of the *alveolar gas equation*.



**Fig. 57.** The relationship between  $P_{AO_2}$  and  $P_{IO_2}$  as described by the alveolar gas equation.

It must be noted that this equation does not make allowance for the contribution of water vapour to the alveolar gas mixture. At body temperature, water vapour contributes a partial pressure of 47 mmHg, so if  $P_{atmos}$  is 760 mmHg the true pressure being contributed by the gases is closer to 713 mmHg.

The equation we have derived also makes at least one nonsensical prediction. Consider the relationship between  $P_{AO_2}$  and  $P_{IO_2}$  (Fig. 57). It does not seem likely that  $P_{AO_2}$  will ever become negative! If the input of  $O_2$  to the circulation is not sufficient to match the output from the circulation, then clearly, the equation becomes invalid and no longer represents the physiology. The  $P_{IO_2}$  at the top of Everest is around 52 mmHg and by this point this simple form of the alveolar gas no longer holds true.

One further point is worth noting. Throughout the derivation of the alveolar gas equation, we implicitly assume that we are working at a fixed lung volume, say the volume at the end of expiration. In reality,  $R$  is always less than 1, i.e.  $V_{CO_2}$  is less than  $V_{O_2}$ . Therefore the amount of matter in the lungs must be constantly decreasing (less  $CO_2$  is being added than  $O_2$  is being removed). Since pressure is directly proportional to the amount of matter present (by the ideal gas law), this

must mean that intra-alevolar pressure is decreasing. This generates an additional pressure gradient for air to enter the lungs. This gradient is present at all times, even at the end of expiration, and serves to stabilise lung volume. This also has the effect of boosting the  $F_{AO_2}$ , and therefore the  $P_{AO_2}$ . It is possible to derive a somewhat more complex form of the alveolar gas equation which takes account of this.

This passive inflow of gas is not just a physiological curiosity but can be of clinical importance. When  $O_2$  consumption is not too high, it is possible to maintain  $P_{aO_2}$  at an adequate level by administering pure  $O_2$  via a face mask, even if the patient is not breathing! In fact, if gas exchange is normal and the patient is fully-oxygenated at the outset, it is the accumulation of  $CO_2$ , rather than a lack of  $O_2$ , which limits this type of ventilation. This in itself can be rather useful in patients recovering from anaesthesia: the increasing  $P_{aCO_2}$  stimulates breathing.

