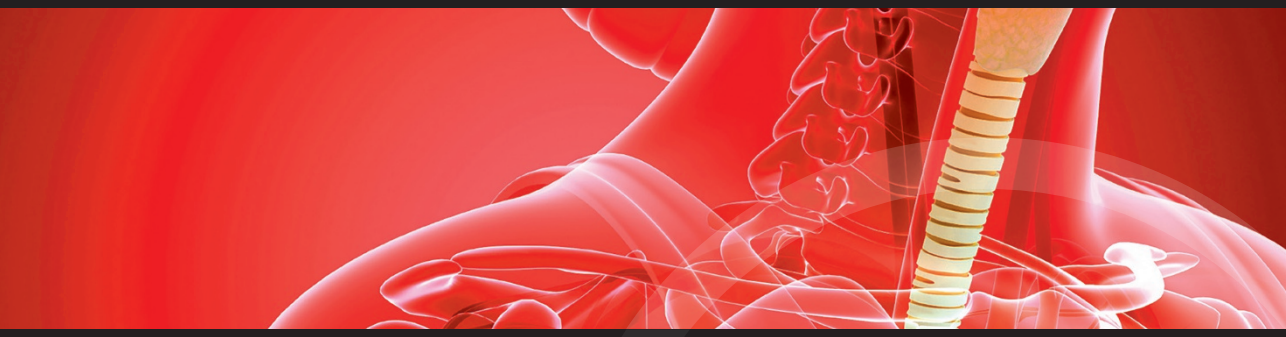
RESPIRATORY MEDICINE

Lecture Notes



Stephen J. Bourke
Graham P. Burns
James G. Macfarlane

10th Edition

with website

WILEY Blackwell

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Lecture Notes

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Stephen J. Bourke

Consultant Physician
Royal Victoria Infirmary
Newcastle upon Tyne, UK

Graham P. Burns

Consultant Physician
Royal Victoria Infirmary
Newcastle upon Tyne, UK

James G. Macfarlane

Consultant Physician
Royal Victoria Infirmary
Newcastle upon Tyne, UK

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Preface

Respiratory Medicine: Lecture Notes was first published in 1975 by our predecessor and colleague, Dr Alistair Brewis, who sadly died in 2014. He was inspirational to generations of students and doctors. From its first edition, *Respiratory Medicine: Lecture Notes* was a classic textbook, opening the eyes of students to the special fascinations of the subject. Many were prompted to pursue a career in respiratory medicine. Subsequent editions mapped the developments in this very broad-ranging specialty, dealing with diseases from cystic fibrosis to lung cancer, COPD to pneumonia, asthma to tuberculosis, sleep disorders to occupational lung diseases.

There have been truly remarkable advances in respiratory medicine over the last 7 years since the previous edition: immunotherapy for lung cancer, monoclonal antibodies for asthma, CFTR modulator therapy for cystic fibrosis and antifibrotic medications for pulmonary fibrosis. New challenges have arisen with a global pandemic of a novel coronavirus SARS-CoV-2.

As *Respiratory Medicine: Lecture Notes* moves towards its half-century in this 10th edition, the text has been revised and expanded to provide a concise up-to-date summary of respiratory medicine for undergraduate students and junior doctors preparing for postgraduate examinations. A particular feature of respiratory medicine in recent years has been multidisciplinary teamwork, utilising skills from a variety of disciplines to provide the best care for patients with respiratory diseases. This book should be useful to colleagues such as physiotherapists, lung function physiologists and respiratory nurse specialists. The emphasis of the book has always been on practical information that is useful and relevant to everyday clinical medicine, and the 10th edition remains a patient-based book to be read before and after visits to the wards and clinics where clinical medicine is learnt and practised. As *Respiratory Medicine: Lecture Notes* has developed over time, students have become teachers and continue to learn by teaching. Each successive generation adds to our understanding and builds on the knowledge of predecessors.

We remain grateful to our teachers and their teachers, and we pass on our evolving knowledge of respiratory medicine to our students and their students.

S.J. Bourke
G.P Burns
J.G. Macfarlane

About the Companion Website

This book is accompanied by a website containing:

www.wiley.com/go/bourke/respiratory10e

- Interactive multiple choice questions
- Figures from the book as PowerPoint slides
- Key points from the book as PDFs

Part 1

Structure and function

1

Anatomy and physiology of the lungs

The anatomy and physiology of the respiratory system are designed in such a way as to bring air from the atmosphere and blood from the circulation into close proximity across the alveolar capillary membrane. This facilitates the exchange of oxygen and carbon dioxide between the blood and the outside world.

A brief revision of clinically relevant anatomy

Bronchial tree and alveoli

The **trachea** has cartilaginous horseshoe-shaped 'rings' supporting its anterior and lateral walls. The posterior wall is flaccid and bulges forward during coughing, for example. This results in narrowing of the lumen, which increases the shearing force from the moving air on the mucus lying on the tracheal walls.

The trachea divides into the right and left main bronchi at the level of the sternal angle (angle of Louis). The **left main bronchus** is longer than the right and leaves the trachea at a more abrupt angle. The **right main bronchus** is more directly in line with the trachea, so that inhaled material tends to enter the right lung more readily than the left.

The main bronchi divide into **lobar bronchi** (upper, middle and lower on the right; upper and lower on the left) and then **segmental bronchi**, as shown in Fig. 1.1. The position of the lungs in relation to external landmarks is shown in Fig. 1.2. **Bronchi** are airways with cartilage in their walls, and there are about 10 divisions of bronchi beyond the tracheal bifurcation. Smaller airways without cartilage in their walls are referred to as **bronchioles**. **Respiratory bronchioles** are peripheral bronchioles with alveoli in their walls. Bronchioles immediately proximal to alveoli are known as **terminal bronchioles**. In the bronchi, smooth muscle is arranged in a spiral fashion internal to the cartilaginous plates. The muscle coat becomes more complete distally as the cartilaginous plates become more fragmentary.

The epithelial lining is ciliated and includes goblet cells. The cilia beat with a whip-like action, and waves of contraction pass in an organised fashion from cell to cell so that material trapped in the sticky mucus layer above the cilia is moved upwards and out of the lung. This 'mucociliary escalator' is an important part of the lung's defences. Larger bronchi also have acinar mucus-secreting glands in the submucosa; these are hypertrophied in chronic bronchitis.

Alveoli are about 0.1– 0.2 mm in diameter and are lined by a thin layer of cells, of which there are two types: type I pneumocytes have flattened processes that extend to cover most of the internal surface of the alveoli; type II pneumocytes are less numerous and contain lamellated structures, which are concerned with the production of surfactant (Fig. 1.3). There is a potential space between the alveolar cells and the capillary basement membrane, which is only apparent in disease states, when it may contain fluid, fibrous tissue or a cellular infiltrate.

Lung perfusion

The lungs receive a blood supply from both the pulmonary circulation and the systemic circulation, via bronchial arteries. The purpose of the pulmonary circulation is to take the entire circulating volume of (deoxygenated) blood through the lungs in order to pick up oxygen and offload carbon dioxide. The

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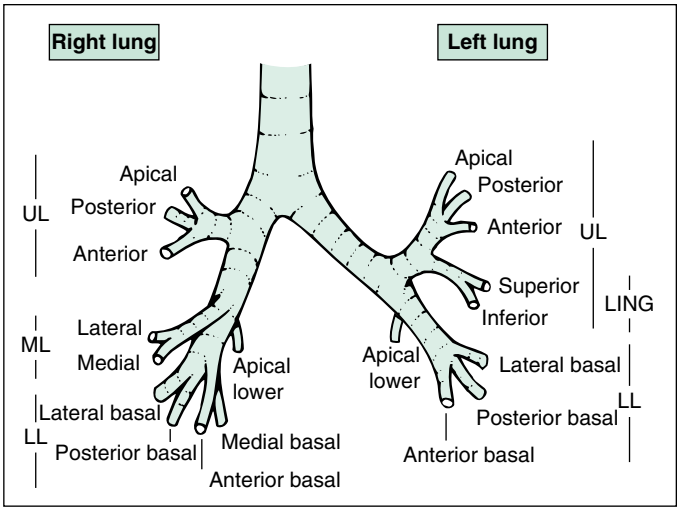

Figure 1.1 Diagram of bronchopulmonary segments. LING, lingula; LL, lower lobe; ML, middle lobe; UL, upper lobe.

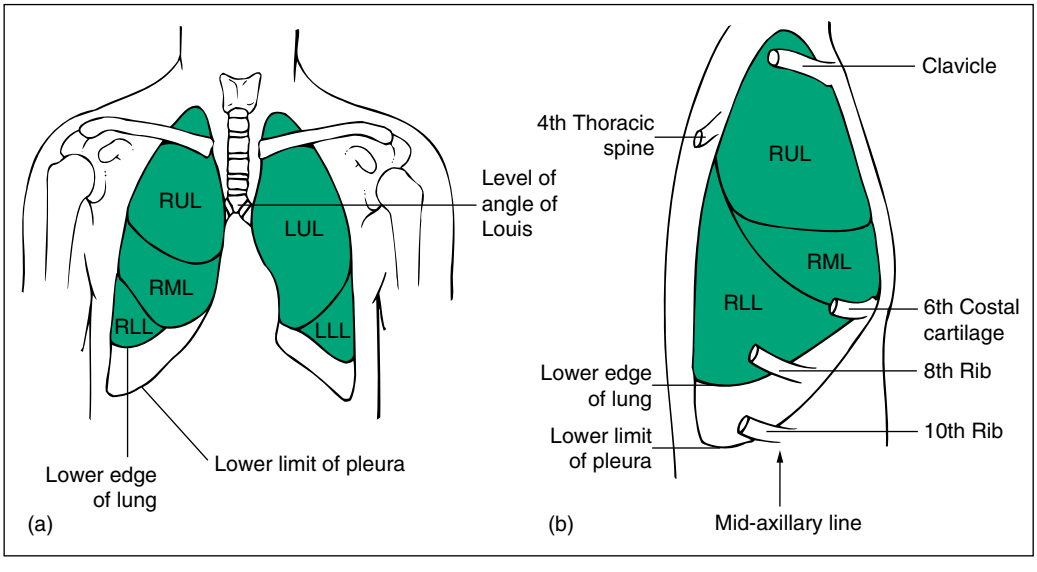

Figure 1.2 Surface anatomy. (a) Anterior view of the lungs. (b) Lateral view of the right side of the chest at resting end-expiratory position. LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

bronchial arteries carry oxygenated blood from the systemic circulation to supply the tissues of the lung.

The **pulmonary artery** arises from the right ventricle and divides into left and right pulmonary arteries, which further divide into branches accompanying the bronchial tree. The pulmonary capillary network in the alveolar walls is very dense and provides a very large surface area for gas exchange. The pulmonary venules drain laterally to the periphery of lung lobules and then pass centrally into the interlobular and intersegmental septa, ultimately joining together to form the four main pulmonary veins, which empty into the left atrium.

Several small **bronchial arteries** usually arise from the descending aorta and travel in the outer layers of the bronchi and bronchioles, supplying the tissues of the airways down to the level of the respiratory bronchiole. Most of the blood drains into

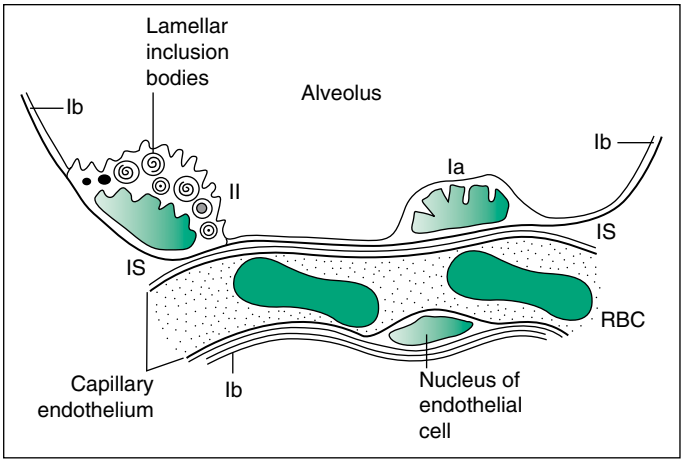

Figure 1.3 Structure of the alveolar wall as revealed by electron microscopy. Ia, type I pneumocyte; Ib, flattened extension of type I pneumocyte covering most of the internal surface of the alveolus; II, type II pneumocyte with lamellar inclusion bodies, which are probably the site of surfactant formation; IS, interstitial space; RBC, red blood corpuscle. Pneumocytes and endothelial cells rest upon thin continuous basement membranes, which are not shown.

radicles of the pulmonary vein, contributing a small amount of desaturated blood, which accounts for part of the 'physiological shunt' (blood passing through the lungs without being oxygenated) observed in normal individuals. The bronchial arteries may undergo hypertrophy when there is chronic pulmonary inflammation, and major haemoptysis in diseases such as bronchiectasis or aspergilloma usually arises from the bronchial rather than the pulmonary arteries and may be treated by therapeutic bronchial artery embolisation. The pulmonary circulation normally offers a much lower resistance and operates at a lower perfusion pressure than the systemic circulation. The pulmonary capillaries may be compressed as they pass through the alveolar walls if alveolar pressure rises above capillary pressure.

Physiology

The core business of the lungs is to bring oxygen into the body and to take carbon dioxide out. The deceptively simple act of 'breathing' comprises two quite distinct processes.

1 **Ventilation.** The movement of air in and out of the lungs (between the outside world and the alveoli).
2 **Gas exchange.** The exchange of oxygen and carbon dioxide between the airspace of the alveoli and the blood.

Ventilation continues throughout life, largely unconsciously, coordinated by a centre in the brain stem. The factors that regulate the process, 'the control of breathing', will also be considered here. Gas exchange happens automatically (by diffusion) if blood and inspired air are brought into close proximity.

Ventilation

To understand this process, we need to consider the muscles that 'drive the pump' and the resistive forces they have to overcome. These forces include the inherent elastic property of the lungs and the resistance to airflow through the bronchi (airway resistance).

The muscles that drive the pump

Inspiration requires muscular work. The diaphragm is the principal muscle of inspiration. At the end of an expiration, the diaphragm sits in a high, domed position in the thorax (Fig. 1.4). To inspire, the strong muscular sheet contracts, stiffens and tends to push the abdominal contents down. There is variable resistance to this downward pressure by the abdomen, which means that in order to accommodate the new shape of the diaphragm, the lower ribs (to which it is attached) also move upwards and outwards. (When airway resistance is present, as in asthma or chronic obstructive pulmonary disease [COPD], the situation is very different; see Chapters 2 & 11.) The degree of resistance the abdomen presents can be voluntarily increased by contracting the abdominal muscles; inspiration then leads to a visible expansion of the thorax, rather than a distension of the abdomen (try it). The resistance may also be increased by abdominal obesity. In such circumstances, there is an involuntary limitation to the downward excursion of the

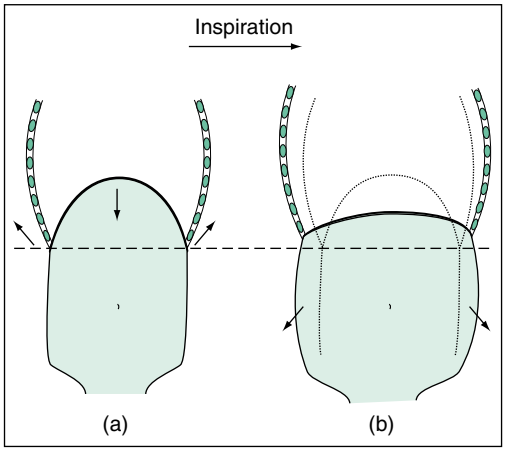

Figure 1.4 Effect of diaphragmatic contraction. Diagram of the ribcage, abdominal cavity and diaphragm showing the position at the end of resting expiration (a). As the diaphragm contracts, it pushes the abdominal contents down (the abdominal wall moves outwards) and reduces pressure within the thorax, which 'sucks' air in through the mouth (inspiration). (b) As the diaphragm shortens and descends, it also stiffens. The diaphragm meets a variable degree of resistance to downward discursion, which forces the lower ribs to move up and outward to accommodate its new position.

diaphragm and, as the potential for upward movement of the ribs is limited, the capacity for full inspiration is diminished. This inability to fully inflate the lungs is an example of a **restrictive ventilatory defect** (see Chapter 3).

Other muscles are also involved in inspiration. The scalene muscles elevate the upper ribs and sternum. These were once considered, along with the sternocleidomastoids, to be '**accessory muscles of respiration**', only brought into play during the exaggerated ventilatory effort of acute respiratory distress. Electromyographic studies, however, have demonstrated that these muscles are active even in quiet breathing, although less obviously so.

The intercostal muscles bind the ribs to ensure the integrity of the chest wall. They therefore transfer the effects of actions on the upper or lower ribs to the whole ribcage. They also brace the chest wall, resisting the bulging or in-drawing effect of changes in pleural pressure during breathing. This bracing effect can be overcome to some extent by the exaggerated pressure changes seen during periods of more extreme respiratory effort, and in slim individuals **intercostal recession** may be observed as a sign of respiratory distress.

Whilst inspiration is the result of active muscular effort, quiet expiration is a more passive process. The inspiratory muscles steadily release their contraction and the elastic recoil of the lungs brings the tidal breathing cycle back to its start point. Forced expiration, however – either volitional or as in coughing – requires muscular effort. The abdominal musculature is the principal agent in this.

The inherent elastic property of the lungs

Lung tissue has a natural elasticity. Left to its own devices, a lung would tend to shrink to little more than the size of a tennis ball. This can sometimes be observed radiographically in the context of a complete **pneumothorax** (see Chapter 16). The lung's tendency to contract is counteracted by the semi-rigid chest wall, which itself has a tendency to spring outward from its usual position. At the end of a normal tidal expiration, the two opposing forces are nicely balanced and no muscular effort is required to hold this 'neutral' position. Breathing at close to this lung volume (normal tidal breathing) is therefore relatively efficient and minimises work. It is rather like gently stretching and relaxing a spring from its neutral, tension-free position. In some diseases (asthma or COPD), tidal ventilation is obliged to occur at higher lung volumes (see Chapter 3). Breathing then is rather like stretching and relaxing a spring that is already under a considerable degree of tension. The **work of breathing** is therefore increased, a factor that contributes to the sensation of breathlessness. Test this yourself: take a good breath in and try to breathe normally at this high lung volume for a minute.

The natural tendencies for the chest wall to spring outwards and the lung to contract down present opposing forces, which generate a negative pressure within the pleural space. This negative pressure ('vacuum') maintains the lung in its stretched state. Clearly, at higher lung volumes, the lung is at greater stretch and a more negative pleural pressure is required to hold it in position. The relationship between pleural pressure (the force on the lung) and lung volume can be plotted graphically (Fig. 1.5). The lung does not behave as a perfect spring, however. You may recall that the length of a spring is proportional to the force applied to it (Hooke's law). In the case of the lung, as its volume increases, greater and greater force is needed to achieve the same additional increase in volume; that is, the lung becomes less 'compliant' as its volume increases. **Lung compliance** is defined as 'the change in lung volume brought about by a unit change in transpulmonary (intrapleural) pressure'.

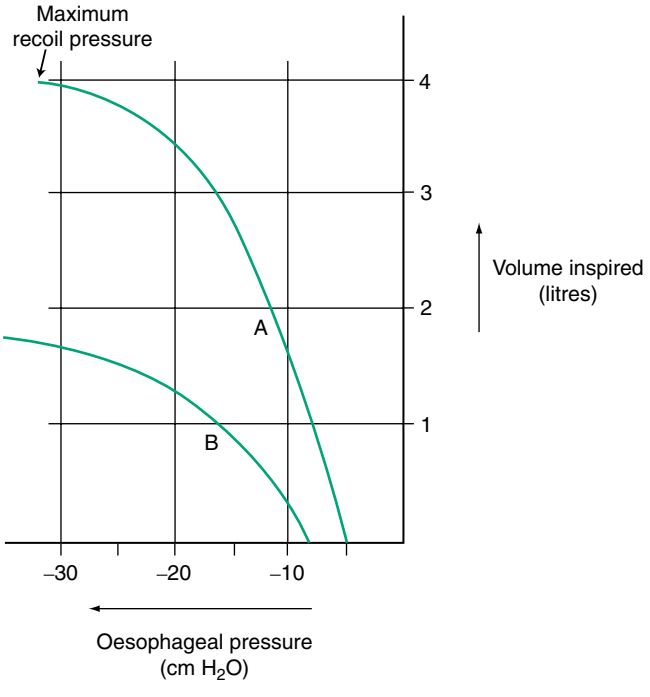

Figure 1.5 Graph of (static) lung volume against oesophageal pressure (a surrogate for intrapleural pressure). In both subjects A and B, we see that lung compliance – the change in lung volume per unit change in intrapleural pressure (or slope of the curve) – is reduced at higher lung volumes. A: normal individual. B: individual with reduced lung compliance, such as lung fibrosis.

Airway resistance

In addition to overcoming the elastic properties of the lungs and the chest wall, during active breathing the muscles of respiration also have to overcome the frictional forces opposing flow up and down the airways.

Site of maximal resistance

It is generally understood that resistance to flow in a tube increases sharply as luminal radius (r) decreases (with laminar flow, resistance is inversely proportional to r^4). It seems rather contradictory, therefore, to learn that in a healthy individual, the greater part of total airway resistance is situated in the large airways (larynx, trachea and main bronchi) rather than in the small airways. This is in part due to the fact that the flow velocity is greatest and flow most turbulent in the central airways, but also due to the much greater *total* cross-sectional area in the later generations of airway (Fig. 1.6). Remember, we only have one trachea, but by the 10th division we have very many small airways, which effectively function in parallel.

Conditions may be different in disease states. Asthma and COPD – diseases that affect airway calibre – tend to have a greater proportionate effect on smaller generations of airway. The reduced calibre of the smaller airways then becomes overwhelmingly important and the site of principal resistance moves distally.

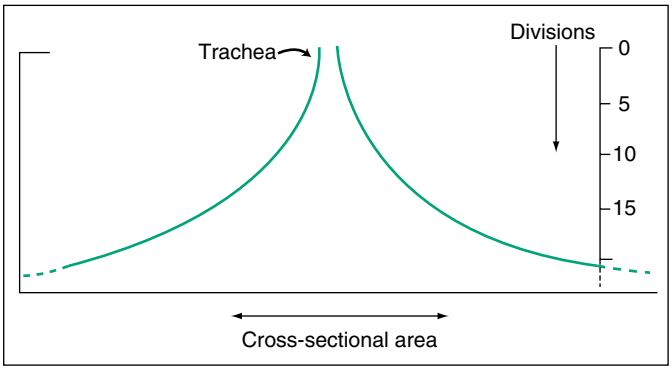

Figure 1.6 Diagrammatic representation of the increase in total cross-sectional area of the airways at successive divisions.

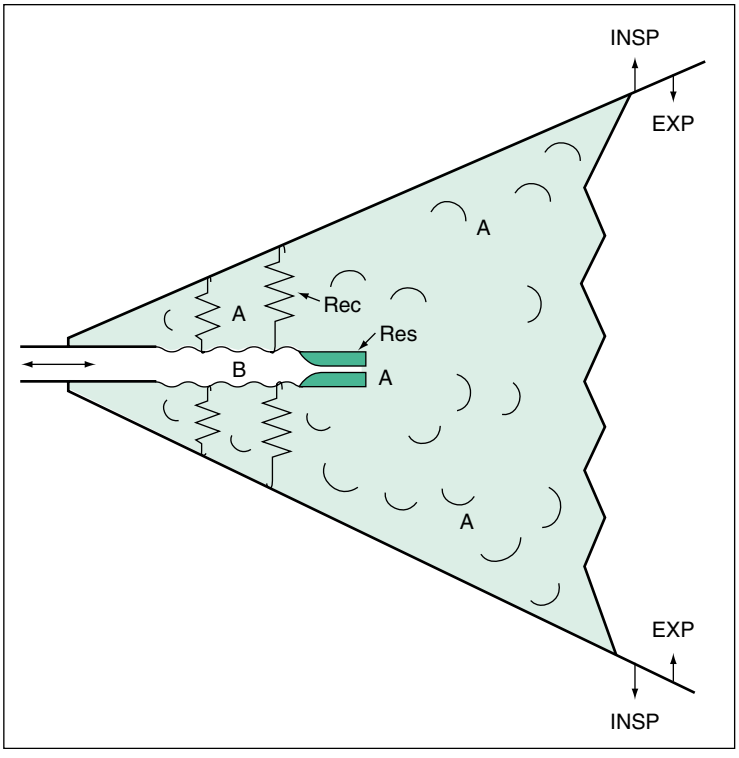

Figure 1.7 Model of the lung, demonstrating the flow-limiting mechanism (see text). The chest is represented as a bellows. The airways of the lungs are represented collectively as having a distal resistive segment (Res) and a more proximal collapsible or 'floppy' segment. The walls of the floppy segment are kept apart by the retractile force of lung recoil (Rec). EXP, expiration; INSP inspiration.

Consider the model of the lung represented in Fig. 1.7. Here, the tube represents a route through generations of airways from the alveoli to the mouth. The smaller generations, without cartilaginous support, are represented by the 'floppy' segment (B). Airways are embedded within the lung and are attached externally to lung tissue whose elastic recoil and ultimate connection to the chest wall supports the floppy segments. This recoil force is represented by the springs.

During expiration, a positive pressure is generated in the alveolar space (A). Air flows from A along the airway, past B, where the pressure is lower (it must be, otherwise the air would not have flowed in this direction), and on to the mouth, where the pressure is nominally 'zero'.

The pressure difference across the walls of the floppy segment (A minus B) would tend to cause this part of the airway to collapse. It is prevented from doing so by the retractile force of lung recoil (tension within the springs).

The flow-limiting mechanism

During expiration, the extent of the pressure drop between A and B is proportional to the flow rate. Clearly, with increased effort, the pressure at A will increase, the pressure difference between A & B will increase and flow rate will be increased . . . up to a point. Eventually, a critical flow rate will be reached, where the pressure gradient between A and B is sufficient to overcome the retractile force of the lung, the airway wall collapses and airflow ceases. Once there is no flow, the pressure inside the airway at point B quickly equilibrates with that at A. With no pressure difference forcing the airway wall to collapse, the retractile force of the lung reopens the airway and flow recommences. This brings us back to where we started and the cycle begins again. It will be apparent that this mechanism determines a maximum possible flow rate along the airway. Any attempt to increase flow rate (associated with a greater pressure difference A to B) will simply result in airway closure. As each route out of the lung will similarly have a maximal possible flow rate, the expiratory flow from the lung as a whole will have an absolute limit. It can be seen that this limit (to expiratory flow) is set by the internal mechanics of the lung, not by muscular strength or effort (above a certain level of effort). That is perhaps fortunate; if it were not the case then lung function tests such as **peak expiratory flow rate** (PEFR) would not be tests of lung function at all, but of muscular strength.

The effects of disease on maximum flow rate

In asthma (see Chapter 10), airway narrowing occurs, leading to a greater resistance between point A (the alveolus) and point B. The pressure drop, A to B, for any given flow rate will therefore be greater than in the healthy lung, and the critical (maximal) flow rate (when the pressure difference between A and B is just enough to overcome the retractile force of the lung) will be lower. You may have known for some time that peak expiratory flow is reduced in asthma, but now you understand why.

In COPD (see Chapter 11), the loss of alveolar walls (emphysema) reduces the elastic recoil of the lung. There is therefore less protective retractile force on the airway wall and the critical pressure drop along the airway required to cause airway collapse will occur at a lower flow rate. Thus, maximum expiratory flow is also reduced in COPD.

Airway resistance and lung volume

It can easily be seen in the model that, as lung volume decreases, lung elastic recoil (tension within the springs) diminishes, providing less and less support for the floppy airway. It is clear, therefore, that the maximum flow rate achievable is dependent on lung volume and is reduced as lung volume is reduced. For any given lung volume, there will be a maximum expiratory flow that cannot be exceeded, no matter what the effort. You can confirm this by inspecting the shape of a flow loop, which is effectively a graph of the maximal flow rate achievable at each lung volume (see Chapter 3). A true PEFR can only be achieved by beginning forced expiration from a position of full inspiration. I would suggest you've been aware of this fact for longer than you realise. Immediately prior to blowing out the candles on your second birthday cake, you probably took a big breath in. At the age of 2, you had an intuitive understanding of the volume dependence of maximal expiratory flow rate.

Lung volume and site of maximal airway resistance

As we have already discussed, the greater part of airway resistance resides in the central airways. These airways are well supported by cartilage and so generally maintain their calibre even at low lung volumes. The calibre of the small airways, without cartilaginous support, is heavily dependent on lung volume. At lower lung volumes, their calibre is reduced, and resistance is increased. During expiration, therefore, as lung volume declines, the site of principal resistance moves from the large central airways to the small peripheral airways. The PEFR (see Chapter 3) tests expiratory flow at high lung volume and is therefore determined largely by the central airways. The **forced expiratory volume in 1 second** (FEV_1; see Chapter 3) is also heavily influenced by the central airway, though not as much as PEFR. Specialised lung function tests that measure expiratory flow at lower lung volumes (e.g. $\mathbf{FEF_{25-75}}$ and $\dot{\mathbf{V}}_{\mathbf{max50}}$; see Chapter 3) therefore provide more information about the smaller airways.

Gas exchange

The lung is ventilated by air and perfused by blood. For gas exchange, to occur these two elements must come into intimate contact.

Where does the air go?

An inspired breath brings air into the lung. That air does not distribute itself evenly, however. Some parts of the lung are more compliant than others, and are therefore more accommodating. This variability in compliance occurs on a gross scale across the lungs (upper zones verses lower zones) and also on a very small scale in a more random pattern. At the gross level, the lungs can be imagined as 'hanging' inside the thorax and resting on the diaphragm; the effect of gravity means that the upper parts of the lungs are under considerable stretch, whilst the bases sit relatively compressed on the diaphragm. During inspiration (as the diaphragm descends) the upper parts of the lung, which were already stretched, cannot expand much more to accommodate the incoming air; the bases, on the other hand, are ripe for inflation. Therefore, far more of each inspired breath ends up in the lower zones than the upper zones.

On a small scale, adjacent lobules or even alveoli may not have the same compliance. Airway anatomy is not precisely uniform either, and airway resistance between individual lung units will vary. It can therefore be seen that ventilation will vary in an apparently random fashion on a small scale throughout the lung. This phenomenon may be rather modest in health, but is likely to be exaggerated in many lung diseases in which airway resistance or lung compliance is affected.

Where does the blood go?

The pulmonary circulation operates under much lower pressure than the systemic circulation. At rest, the driving pressure is only on the order of 15 mmHg.

In the upright posture, therefore, there is barely enough pressure to fill the upper parts of the system and the apices of the lung receive very little perfusion at all from the pulmonary circulation. The relative over perfusion of the bases mirrors the pattern seen with ventilation (which is fortunate, if our aim is to bring blood and air into contact), but the disparity is even greater in the case of perfusion. Thus, at the bases of the lungs, perfusion exceeds ventilation, while, at the apices, ventilation exceeds perfusion.

The distribution of perfusion is also heavily influenced by another factor: hypoxia. By a mechanism we do not fully understand, low oxygen levels in a region of the lung have a direct vasoconstrictor effect on the pulmonary artery supplying that region. This has the beneficial effect of diverting blood away from the areas of lung that are poorly ventilated towards the well-ventilated areas. This 'automatic' **ventilation/perfusion (V/Q) matching system** aims to maximise the contact between air and blood and is critically important to gas exchange.

Relationship between the partial pressures of O_2 and CO_2

During steady-state conditions, the relationship between the amount of carbon dioxide produced by the body and the amount of oxygen absorbed depends upon the metabolic activity of the body. This is referred to as the 'respiratory quotient' (RQ).

$$RQ = \frac{CO_2 \text{ produced}}{O_2 \text{ absorbed}}$$

The actual value varies from 0.7 during pure fat metabolism to 1.0 during pure carbohydrate metabolism. The RQ is usually about 0.8, and it is assumed to be such for everyday clinical calculations.

Carbon dioxide

If carbon dioxide is being produced by the body at a constant rate then the partial pressure of CO_2 (PCO_2) of alveolar air (written P_ACO_2) depends only upon the amount of outside air with which the carbon dioxide is mixed in the alveoli; that is, it depends only upon alveolar ventilation. If alveolar ventilation increases, P_ACO_2 will fall; if alveolar ventilation decreases, P_ACO_2 will rise. P_ACO_2 (as well as arterial PCO_2, written P_aCO_2) is a sensitive index of alveolar ventilation.

Oxygen

The partial pressure of alveolar O_2 (P_AO_2) also varies with alveolar ventilation. If alveolar ventilation increases greatly then P_AO_2 will rise and begin to approach the PO_2 of the inspired air. If alveolar ventilation is reduced, P_AO_2 will also be reduced. Whilst arterial PO_2 (written P_aO_2) also varies with alveolar ventilation (in the same direction as alveolar PO_2), it is not a reliable index of alveolar ventilation, as it is also profoundly affected by regional changes in V/Q matching (see later in this chapter).

The possible combinations of PCO_2 and PO_2 in alveolar gas are shown in Fig. 1.8. Moist atmospheric air at 37 °C has a PO_2 is between 20 and 21 kPa. In this model, oxygen can be exchanged with carbon dioxide in the alveoli to produce any combination of P_AO_2 and

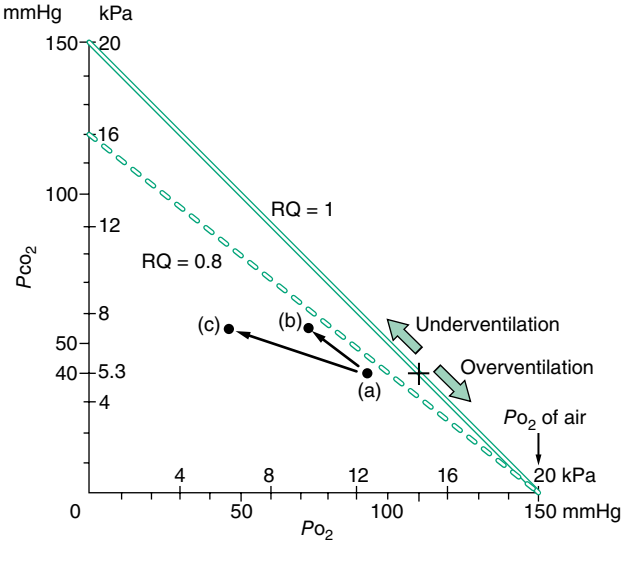

Figure 1.8 Oxygen–carbon dioxide diagram. The continuous and interrupted lines describe the possible combinations of PCO_2 and PO_2 in alveolar air when the RQ is 1 versus 0.8. When the alveolar gas composition is represented by '+' then (a) represents the partial pressures in arterial blood. With progressive underventilation the arterial blood pressures would change to (b). At (c) the PO_2 is lower than can be accounted for by underventilation alone.

P_ACO_2 described by the oblique line which joins P_AO_2 20 kPa and P_ACO_2 20 kPa. The position of the cross on this line represents the composition of a hypothetical sample of alveolar air. A fall in alveolar ventilation will result in an upward movement of this point along the line; conversely, an increase in alveolar ventilation will result in a downward movement of the point.

In practice, RQ is not 1.0 but closer to 0.8. In other words:

$$\text{alveolar}\,Po_2 + \left(\frac{\text{alveolar}\,Pco_2}{0.8}\right) = 20\,\text{KPa}$$

This is represented by the dotted line in Fig. 1.8.

Point (a) represents the PCO_2 and PO_2 of **arterial blood** (it lies a little to the left of the RQ 0.8 line because of the small normal alveolar–arterial oxygen tension difference). Point (b) represents the arterial gas tension following a period of underventilation. If the P_aCO_2 and P_aO_2 were those represented by point (c), this would imply that the fall in P_aO_2 was more than could be accounted for by reduced alveolar ventilation alone. This would indicate a problem with V/Q matching and thus gas exchange (see below and Chapter 3).

The carriage of CO_2 and O_2 by blood

Blood will carry different quantities of a gas when it is at different partial pressures, as described by a dissociation curve. The dissociation curves for oxygen and carbon dioxide are very different (they are shown together on the same scale in Fig. 1.9). The amount of carbon dioxide carried by the blood is roughly proportional to the P_aCO_2 over the whole range normally encountered, whereas the quantity of oxygen carried is only proportional to the P_aO_2 over a very limited range of about 3–7 kPa (22–52 mmHg). Above 13.3 kPa (100 mmHg), the haemoglobin is fully saturated. Further increases in partial pressure result in hardly any additional oxygen being carried.

Effect of local differences in V/Q

In the normal lung, the vast majority of alveoli receive ventilation and perfusion in about the correct proportion (Fig. 1.10a). In diffuse disease of the lung, however, it is usual for ventilation and perfusion to be irregularly distributed, so that a greater scatter of V/Q ratios is encountered (Fig. 1.10b). Even if the overall V/Q remains normal, there is wide local variation in V/Q. Looking at Fig. 1.10, it is tempting to suppose the effects of the alveoli with low V/Q might be nicely balanced by the alveoli with high V/Q. In fact, this is not the case: the increased range of V/Q within the lung affects the transport of CO_2 and O_2 differently.

Fig. 1.11b and c show regions of low and high V/Q, respectively, while Fig. 1.11d shows the result of mixing blood from these two regions. Fig. 1.11a shows normal V/Q, for contrast.

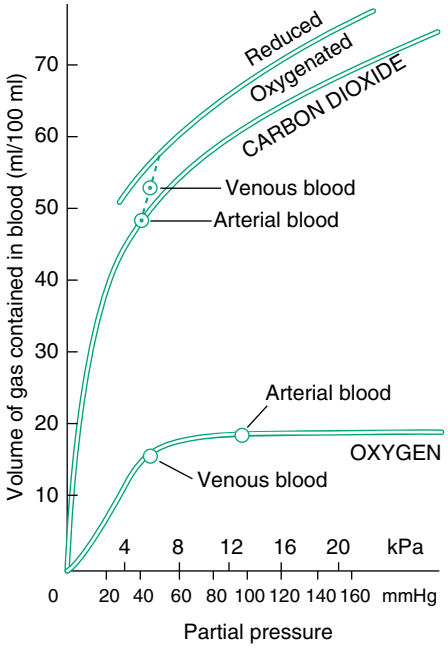

Figure 1.9 Blood oxygen and carbon dioxide dissociation curves drawn to the same scale.

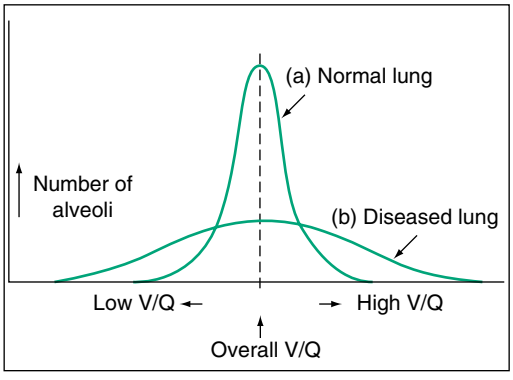

Figure 1.10 Distribution of V/Q relationships within the lungs. Although the overall V/Q ratio is the same in the two examples shown, the increased spread of V/Q ratios within the diseased lung (b) will result in a lower arterial oxygen tension and content than in the normal lung (a). Arterial PCO_2 will be similar in both cases.

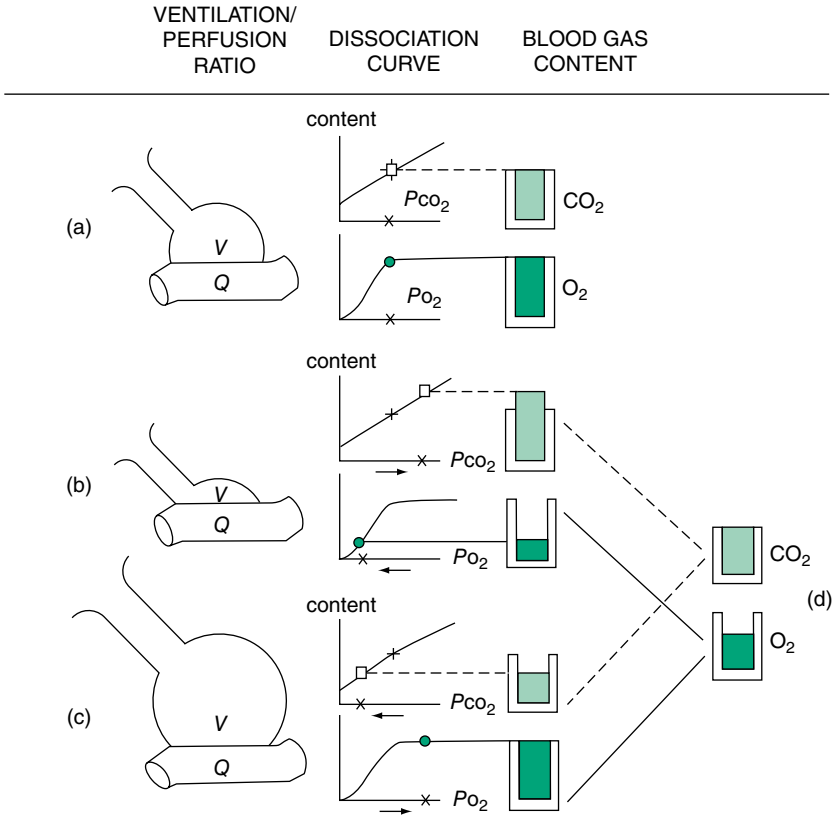

Figure 1.11 Effect of V/Q imbalance. (a) Appropriate V/Q. The V/Q ratio is shown diagrammatically on the left. When ventilation is appropriately matched to perfusion in an alveolus or in the lung as a whole, the PCO_2 is about 5.3 kPa (40 mmHg) and the PO_2 is about 12.6 kPa (95 mmHg). The dissociation curves shown in the centre of the diagram describe the relationship between the blood gas tension and the amount of gas carried by the blood. The normal blood gas contents are represented very diagrammatically on the right. (b) Low V/Q. Reduced ventilation relative to blood flow results in a rise in arterial PCO_2 and a fall in PO_2. Reference to the dissociation curves shows that this produces a rise in arterial CO_2 content and a fall in O_2 content. (c) High V/Q. Increased ventilation relative to blood flow results in a fall in PCO_2 and a rise in PO_2. Reference to the dissociation curves shows that this results in a fall in CO_2 content below the normal level but no increase in O_2 content. In health, the vast majority of alveoli have an appropriate balance of ventilation and perfusion and the arterial blood has a normal CO_2 and O_2 content, as shown in (a). In many disease states, the V/Q ratio varies widely between areas. Such variation always results in a disturbance of blood gas content. The effects of areas of low V/Q are not corrected by areas of high V/Q. The result of mixing blood from areas of low and high V/Q is shown diagrammatically on the extreme right (d). It can be seen that, with respect to CO_2 content, the high content of blood from underventilated areas is balanced by the low content from overventilated areas. However, in the case of O_2, the low content of blood from underventilated areas cannot be compensated for by an equivalent increase in the O_2 content of blood from overventilated areas. *Arterial hypoxaemia is inevitable if there are areas of low V/Q (relative underventilation or overperfusion*).

Effect on arterial CO_2 content

Blood with a high CO_2 content returning from low-V/Q areas mixes with blood with a low CO_2 content returning from high-V/Q areas. The net CO_2 content of arterial blood may be near normal, as the two balance out.

Effect on arterial O_2 content

Here the situation is different. Blood returning from low-V/Q areas has a low PO_2 and low O_2 content, but there is a limit to how far this deficit can be made good by mixture with blood returning from high-V/Q areas. Blood returning from a high-V/Q area will have

a high PO_2 but is unable to carry more than the 'normal' quantity of oxygen, as the haemoglobin will already be saturated.

- Areas of low V/Q result in a rise in arterial CO_2 and a fall in arterial O_2 content.
- Increased ventilation in areas of high V/Q may balance the effect on CO_2 content but will only partially correct the reduction in O_2 content; a degree of hypoxaemia is inevitable.
- It follows that, where arterial oxygen levels are lower than would be expected from consideration of P_aCO_2 (overall ventilation) alone, there must be a disturbance to the normal V/Q matching system in the lung; that is, there is likely to be an intrinsic problem with the lung or its vasculature.

When interpreting arterial blood gas results, it is often important to know whether an observed low P_aO_2 can be explained by underventilation alone or whether a problem with the lung or pulmonary vasculature is present. The tool we use for this task is the **alveolar gas equation**.

The alveolar gas equation

An understanding of the relationship between P_aCO_2 and P_aO_2 is critical to the interpretation of blood gases (see Chapter 3). The relationship can be summarised in an equation known as the alveolar gas equation.

- Pure underventilation leads to an increase in P_aCO_2 and a 'proportionate' fall in P_aO_2. This is known as **type 2 respiratory failure**.
- A disturbance in V/Q matching leads to impaired gas exchange with a fall in P_aO_2 but no change in P_aCO_2. This is known as a **type 1 respiratory failure**.
- Because these two problems can occur simultaneously, the alveolar gas equation is needed to determine whether an observed fall in P_aO_2 can be accounted for by underventilation alone or whether there is also an intrinsic problem with the lungs (impairing gas exchange).

Rather than merely memorise the alveolar gas equation, spend just a moment here understanding its derivation (this is *not* a rigorous mathematical derivation, merely an attempt to impart some insight into its meaning).

Imagine a lung, disconnected from the circulation, being ventilated. Clearly, in a short space of time, P_AO_2 will come to equal the partial pressure of oxygen in the inspired air (P_IO_2):

$$P_Ao_2 = P_Io_2$$

In real life, the pulmonary circulation is in intimate contact with the lungs and is continuously removing O_2 from the alveoli. The alveolar partial pressure of O_2 is therefore equal to the partial pressure in the inspired air minus the amount removed.

If the exchange of oxygen for carbon dioxide were a 1:1 swap then the amount of O_2 removed would equal the amount of CO_2 added to the alveoli and the equation would become:

$$P_Ao_2 = P_Io_2 - P_Aco_2$$

The CO_2:O_2 exchange, as already discussed, is, however, not usually 1:1. The RQ is usually taken to be 0.8.

Thus:

$$P_Ao_2 = P_Io_2 - (P_Aco_2 / 0.8)$$

As CO_2 is a very soluble gas, P_ACO_2 is virtually the same as P_aCO_2. P_aCO_2 (available from the blood gas measurement) can therefore be used in the equation in place of P_ACO_2:

$$P_Ao_2 = P_Io_2 - (P_aco_2 / 0.8)$$

This is (the simplified version of) the alveolar gas equation. If P_IO_2 is known then P_AO_2 can be calculated.

But, so what? What do we do with the P_AO_2?

Unlike in the case of CO_2, there is normally a difference between alveolar and arterial PO_2 (which should be the greater?). The difference $P_AO_2 - P_aO_2$ is often written $P_{A\text{–}a}O_2$ and is known as the **alveolar–arterial (A–a) gradient**. In healthy young adults, breathing air, this gradient is small; it would be expected to be comfortably less than 2 kPa. If the gradient is greater than this then the abnormality in the blood gas result cannot be accounted for by a change in ventilation alone; there must be an abnormality intrinsic to the lung or its vasculature causing a disturbance of V/Q matching. For examples, see the multiple choice questions at the end of the chapter.

The control of breathing

To understand this, we first have to remember why we breathe. Whilst oxygen is an essential requirement for life, we do not need the high level of oxygenation usually seen in health for survival. We operate with a substantial margin of safety. This safety margin allows us to vary our ventilation (sometimes at the expense of a normal oxygen level) in order to precisely regulate the CO_2 content of the blood. CO_2 is intimately linked with pH. Whilst it is possible to live for years with lower than normal oxygen levels, we cannot survive long at all with pH outside the normal range. Keeping

pH in the normal range is therefore the priority, and CO_2 rather than O_2 is the principal driver of ventilation.

In health, PCO_2 is maintained at very close to 5.3 kPa (40 mmHg). Any increase above this level provokes hyperventilation; any dip leads to hypoventilation. In practice, PCO_2 is so tightly regulated that such fluctuations are not observable. Even when substantial demands are placed on the respiratory system, such as hard physical exercise (with its dramatic increase in O_2 utilisation and CO_2 production), the arterial PCO_2 will barely budge.

Like any finely tuned sensor, however, if the respiratory system is exposed to concentrations it's not designed to deal with for long periods, it will tend to break. In some patients with chronic lung disease (commonly COPD), the CO_2 sensor begins to fail. Underventilation then occurs, and, over time, PCO_2 drifts upward (and PO_2 downward). Despite the fall in PO_2, initially at least, nothing much happens. Although there is a separate sensor monitoring levels of hypoxia, it remains blissfully unconcerned by modest reductions in PO_2 (because of the margin of safety just discussed). Only when PO_2 reaches a levels that could have an impact on bodily function (around 8 kPa; 60 mmHg) does the hypoxic sensor wake up and decide to take action. Happy to tolerate a certain degree of hypoxia, it won't allow the PO_2 to fall below this important threshold, which is marginal to the sustainability of life.

When this occurs, hypoxia then takes up the reins as the driver to ventilation and prevents what would have been a progressive decline to death. Once an individual is dependent on this '**hypoxic drive**,' a degree of hypoxia is (obviously) necessary to drive ventilation. This is not always appreciated. At times, a 'high-flow' oxygen mask may be applied to a patient by a well-meaning doctor in an attempt to raise the PO_2 to a more 'normal' level. But no hypoxia means no drive to breathe. The result can be catastrophic underventilation, which, if not dealt with properly, can be fatal. When treating hypoxic patients who may have chronic lung disease, until their ventilatory drive is known (from arterial blood gas analysis), oxygen should be judiciously controlled to achieve an oxygen saturation (based on pulse oximetry) between 88% and 92%. In this 'Goldilocks' zone, the patient will not die of hypoxia and ventilation is unlikely to be depressed to any significant degree.

KEY POINTS

- The essential function of the lungs is the exchange of oxygen and carbon dioxide between the blood and the atmosphere.
- Ventilation is the process of moving air in and out of the lungs, and it depends on the tidal volume, respiratory rate, resistance of the airways and compliance of the lungs. A fall in ventilation leads to a rise in PCO_2 and a fall in PO_2: type 2 respiratory failure.
- Derangement in the matching of ventilation and perfusion in the lungs (which may be caused by any disease intrinsic to the lung or its vasculature) leads to a fall in PO_2: type 1 respiratory failure.
- The respiratory centre in the brain stem is responsible for the control of breathing. pH and PCO_2 are the primary stimuli to ventilation. Hypoxia only acts as a stimulant when PO_2 < about 8 kPa.

FURTHER READING

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Multiple choice questions

1.1 The principal muscle(s) involved in inspiration is (are):

A the diaphragm

B rectus abdominis

C the scalene muscles

D sternocleidomastoids

E the intercostals

1.2 Lung compliance:

A is reduced as lung volume increases

B is reduced in emphysema

C is increased in lung fibrosis

D is the change in pleural pressure per unit change in lung volume

E is the principal factor determining forced expiratory flow

1.3 In relation to airway resistance:

A overall airway resistance increases as lung volume increases

B in health, at high lung volume, the greater part of airway resistance is situated in the central airways

C airway resistance is reduced in emphysema due to diminished retractile force on the airway

D airway resistance is proportional to the cubed power of the radius of the airway (r^3)

E forced expiratory flow is unrelated to effort

1.4 In relation to ventilation (V) and perfusion (Q):

A the upper zones of the lungs are ventilated more than the lower zones

B the upper zones of the lungs receive more perfusion than the lower zones

C V/Q is greater in the lower zones

D VQ matching is essential to gas exchange

E reduced overall ventilation leads to a fall in PCO_2

1.5 In a patient breathing room air at sea level, the arterial blood gases were: pH 7.36, PCO_2 3.2 kPa, PO_2 12 kPa, $aHCO_3^-$ 19, base excess –5. The alveolar–arterial gradient is:

A 2.5 kPa

B 5.0 kPa

C 5.5 kPa

D 6.5 kPa

E 10.0 kPa

1.6 During expiration, the diaphragm:

A rises

B remains unchanged

C shortens

D stiffens

E causes a fall in intrathoracic pressure

1.7 A reduction in ventilation leads to:

A a rise in P_aCO_2 and P_aO_2

B a fall in P_aCO_2 and P_aO_2

C a rise in P_aCO_2 and a fall in P_aO_2

D a fall in P_aCO_2 and a rise in P_aO_2

E a rise in P_aCO_2 and no change in P_aO_2

1.8 VQ mismatching leads to:

A a rise in P_aCO_2 and no change in P_aO_2

B a fall in P_aCO_2 and P_aO_2

C a rise in P_aCO_2 and a fall in P_aO_2

D a fall in P_aCO_2 and a rise in P_aO_2

E no change in P_aCO_2 and a fall in P_aO_2

1.9 In relation to the control of breathing:

A hypoxia is irrelevant

B a rise of 0.2 kPa in pCO_2 is required before ventilation is driven to increase

C a metabolic acidosis can increase ventilation and therefore P_aO_2

D a fall in blood pH will tend to reduce ventilation

E a fall in pH implies there has been a reduction in ventilation

1.10 In relation to airway resistance:

A resistance is unrelated to lung volume

B the site of principal resistance moves to the smaller airways as lung volume is reduced

C maximum forced expiratory flow can be achieved at mid lung volume

D $FEF_{25–75}$ provides accurate information on the calibre of the large airways

E $FEF_{25–75}$ provides accurate information on the calibre of the small airways

Multiple choice answers

1.1 A

The diaphragm is the main muscle of inspiration; contraction forces the abdominal contents down, creating a relative vacuum in the thorax which 'sucks' air into the lungs.

1.2 A

Lung compliance is the change in lung volume brought about by a unit change in transpulmonary (intrapleural) pressure. The fibrotic lung is less compliant. The emphysematous lung is more compliant. In any lung, its capacity to stretch (expand) is reduced as volume increases ie it gets less compliant.

1.3 B

Airway resistance in health resides principally in the central (large) airways at high lung volume ('You only have one trachea'). As lung volume decreases, the site of greatest resistance moves peripherally to the smaller airways (their calibre diminishes). It is increased in emphysema and is proportional to r^4. Increasing effort WILL lead to increased expiratory flow, but only up to a certain point, beyond which 'peak flow' cannot be increased no matter what the effort.

1.4 D

Gas exchange is driven by diffusion and therefore dependent on bringing the air and blood together (V/Q matching). Most of the ventilation goes to the bases, but an even greater proportion of the perfusion goes to the bases. Poor V/Q leads to a fall in PO_2 but does not affect PCO_2. Reduced overall ventilation causes a rise in PCO_2 and a fall in PO_2.

1.5 B

$$P_AO_2 = P_IO_2 - \frac{P_ACO_2}{0.8}$$

$$P_AO_2 = 21 - \frac{3.2}{0.8} = 17$$

$$P_AO_2 - P_aO_2 = 17 - 12 = 5$$

This is elevated, implying a problem with VQ matching within the lung.

1.6 A

During inspiration, the diaphragm contracts and stiffens, pushing the abdominal contents down and reducing pressure in the thorax, which 'sucks' air in. Expiration is a relatively passive reversal of the process.

1.7 C

Reducing ventilation means less CO_2 is 'blown off' (leading to a rise in P_ACO_2 and P_aCO_2). If fresh air isn't brought into the lungs then alveolar oxygen will not be replenished, P_AO_2 will fall and so must P_aO_2.

1.8 E

See Figure 1.11.

1.9 C

The sensitivity to changes in pH and pCO_2 is so exquisite that adjustments are made before any measurable change can occur. Hypoxia does matter, but only has significant impact on the drive to breathe when pO_2 falls significantly (approx. 8 kPa). A low pH can be caused by either reduced ventilation or a metabolic disturbance (in which case, it would lead to a rise in ventilation). Increased ventilation will increase P_AO_2 and therefore P_aO_2 though it won't increase the oxygen content of the blood (much) as arterial blood is ordinarily close to fully saturated.

1.10 B

As lung volume is reduced, the small airways narrow and the site of principal resistance moves peripherally (i.e. to the smaller airways). Resistance is lowest (and therefore max forced flow rate is achieved) when the lungs are full. FEF_{25-75} provides information on the calibre of the small airways, but it can be a rather noisy signal.

Part 2

History taking, examination and investigations