

1

The respiratory system

Learning strategy

In this chapter we will consider the essential 'must know' facts and concepts of the respiratory system. Our main strategy would involve an exploration of these key principles by following several clinical scenarios.

The first scenario, an asthma attack will introduce us to the anatomy of the respiratory system. A consideration of the pathophysiology of asthma, will lead to a review of the immune system and the mechanism of Type 1 hypersensitivity.

Breathing difficulties will lead us to consider the mechanism of breathing and lung compliance. Lung volumes and capacities will be discussed as we consider the lung function tests of the asthmatic patient. We will also review the key drugs used in asthma treatment.

A second scenario – COPD – leads us to a consideration of acidosis and alkalosis. We will also discuss some key respiratory infections and the important concepts of V/Q mismatch and dead space. Finally we will consider gas exchange, oxygen and carbon dioxide saturation curves and the central and peripheral control of respiration.

Throughout, we will also consider the pathophysiological mechanisms of several key disease states involving the respiratory system, which will, in addition to highlighting the key pathophysiological principles, further reinforce basic principles of anatomy, physiology and pharmacology relevant to the respiratory system.

Try to answer the questions and try to complete the Learning Tasks. The Trigger Boxes should be used as a guide for further reading and revision. At the end of this chapter you should have a sound understanding of the key facts and concepts underlying the respiratory system.

Zoe's breathing difficulties...

It happened again on Boxing Day. Around 5pm Zoe was sitting on her bed reading when she started to become breathless. Breathing was always her 'problem' and Zoe couldn't understand it.

'After all it's supposed to be such a simple thing to do isn't it?' she had asked Mary. 'It's supposed to be automatic isn't it? I mean you just breathe in and out. So why is it such an effort sometimes?'

Zoe took a puff out of her blue inhaler. She wondered if her problems had something to do with the fact that she had been a premature baby and that that she had to be delivered at 33 weeks, by caesarean section.

'Maybe my lungs weren't developed properly' she thought.



What is in Zoe's blue inhaler?

Although Zoe was a premature baby, she didn't have any problems and grew into a healthy child. Had she been born around, say, 26 weeks she would have had serious problems because her respiratory system would have been underdeveloped.

So, let us begin by reviewing the key stages in the development of the respiratory system. First, in terms of origins, the epithelium of the nasopharynx, trachea, bronchi, bronchioles and alveoli are derived from endoderm. The associated cartilage and muscle are mesodermal in origin.



You are expected to know the embryological origins of key anatomical structures. Construct a table listing the main derivatives of endoderm, ectoderm and mesoderm.

So what are the key embryological events in the development of the respiratory system? The respiratory system starts off as an outgrowth of the foregut. In the 4th week the oesophagotracheal septum separates the foregut into the respiratory diverticulum (lung bud) and oesophagus (Figure 1.1). The bud elongates and then branches into two. Each of these two new buds will become the primary bronchus of each lung.



What happens if the diverticulum fails to separate completely from the foregut

What is a TOF (tracheo-oesophageal fistula)?

The left lung bud develops into two secondary bronchi and eventually forms two lobes; the right bud forms three secondary bronchi and three lobes. The tertiary bronchi create the bronchopulmonary segments.

Gas exchange between blood and air in the primitive alveoli is possible in the seventh month of gestation. Lung growth after birth is mainly due to an increase in the number of respiratory bronchioles and alveoli and not due to an increase in size of alveoli. New alveoli are formed for at least 10 years of postnatal life.

What do we mean by the term 'gas exchange'?

Before birth, the lungs are filled with fluid containing surfactant mainly made up of dipalmitoyl phosphatidylcholine, which is produced by type II epithelial cells. When

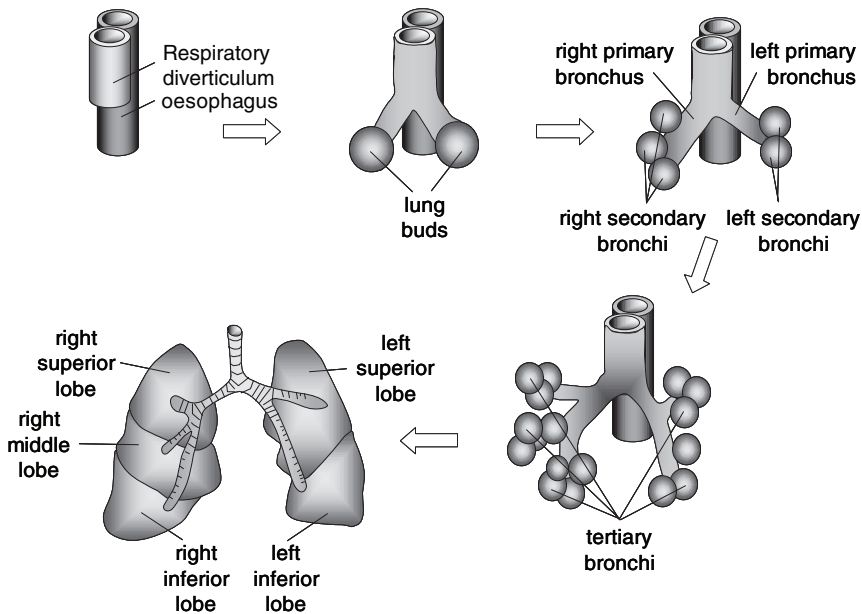


Figure 1.1 Development of the respiratory system. Adapted from Tortora and Grabowski (2003), principles of Anatomy and Physiology, 10th edition, John Wiley & Sons Inc. p.842

respiration begins, lung fluid is reabsorbed but leaves a surfactant coating. If Zoe was born around 26 weeks, her surfactant levels would have been low. She would suffer from respiratory distress syndrome (RDS). Her lungs would be difficult to expand and during deflation her alveoli would collapse. Surfactant decreases the alveolar surface tension and helps the alveoli to expand more easily.

?

What are type I and II pneumocytes? Where do you find them?

Mothers of premature babies are treated with steroids. Why?

What treatment can be given to a 28-week premature baby having difficulty inflating its lungs?

Trigger box Respiratory distress syndrome (RDS)

Deficiency of surfactant causes alveolar collapse and poor gas exchange.

Majority of infants born before 28 weeks develop RDS within 4 hours of birth.

Features: Tachypnoea, cyanosis, diaphragm, subcostal and intercostal retraction, grunting.

CXR: Reticulogranular appearance with air bronchograms.

Treatment: Glucocorticoids to mother, exogenous surfactant, oxygen, continuous positive airway pressure (CPAP), artificial ventilation.

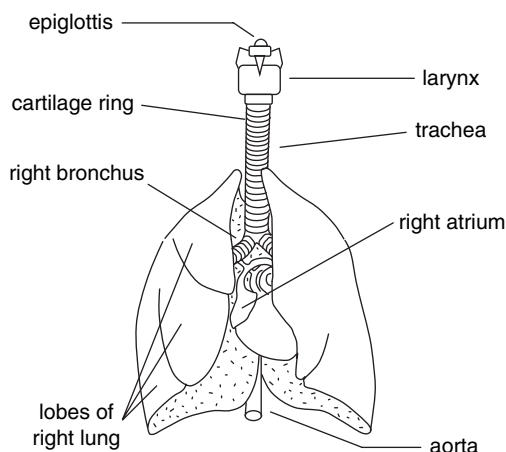


Figure 1.2 Anatomy of the respiratory system. Adapted from Mackean (1969), *Introduction to Biology*, 4th edition, John Murray, London, p.69.

Next let us consider the gross anatomy of the respiratory system. Figure 1.2 shows the important anatomical structures you need to know.

Note that the right lung has three lobes; the left has two. Each lung lobe is made up of bronchopulmonary segments. Label the oblique and horizontal fissures. The right main bronchus is straighter and shorter than the left main bronchus. This helps to explain why Zoe's brother John, at age 4, got a small peanut stuck in the right main bronchus when he inhaled it.

When Zoe's great-uncle Arthur suffered from a really nasty bout of pulmonary tuberculosis the surgeons had to remove several of his bronchopulmonary segments. This was not too difficult because each bronchopulmonary segment is served by its own arteries and vein and is partitioned from other segments by connective tissue.



Define what is meant by the terms (a) 'respiratory bronchiole' and (b) 'terminal bronchiole'.

Let us look at the other main structures that make up the respiratory system. Important structures to know include the nasopharynx, oropharynx, larynx, glottis and trachea. The blood supply of the lungs consists of the pulmonary arteries that run with the airways, the bronchial arteries that branch off from the aorta, and the pulmonary veins that run in the connective tissue septa.

What kind of blood (oxygenated, deoxygenated) is found in these different vessels?

Bronchi have cartilage whereas bronchioles do not. They both have smooth muscle – what is the relevance of these facts to asthma?

Lung connective tissue contains lots of elastic tissue – what is the significance of this elasticity?

The lungs are covered by visceral pleura. This is separated from the parietal pleura which covers the inside of the chest wall by the interpleural space.



What is pleurisy

Trigger box Pleural effusions

Transudate: (protein <30 g/L; LDH <200 iu/l):

Congestive heart failure (CHF), hypothyroidism, nephrotic syndrome

Exudate: (protein >30 g/L; LDH >200 iu/l):

Pneumonia, carcinoma, tuberculosis (TB), pulmonary infarct.

Can detect clinically if >500mL; by CXR >300mL.

Findings: Reduced chest movements, stony dull percussion, decreased breath sounds, reduced vocal resonance. Blunting of costophrenic angle on CXR.

Treatment: drain exudates, treat underlying cause of transudate.

Sclerosing agents to reduce recurrent malignant pleural effusions.

Three years ago Dr Smith, Zoe's GP, had told her that she had asthma. Zoe was also told that this was related to her tendency to suffer from allergies. Also, colds, he stated, can lead to an asthma attack – and she got plenty of those especially in winter.

'The problem is with your immune system' Dr Smith said.

'What's wrong with my immune system?' Zoe asked. 'Isn't it supposed to defend me, zap these nasty bugs?'

'Your immune system is reacting inappropriately to certain antigens' replied Dr Smith and then went on to explain how her immune system was causing her asthma and allergic reactions.

This leads us to introduce the basics of the immune system, which needs to be understood in order to appreciate the pathophysiology of Zoe's asthma. This important system will be considered in detail in Chapter 10 but Figure 1.3 will help to explain what is meant by appropriate and inappropriate immune responses.

Note the central role of the Th cell and the Tc response that can eliminate viruses. This is an *appropriate* immune response. Type I hypersensitivity on the other hand, is an *inappropriate* immune response brought about by the generation of IgE reagenic antibodies against allergens, which leads to mast cell degranulation and the release of mediators that give rise to inflammation and the asthmatic symptoms. Goodpasture's syndrome is a type II hypersensitivity reaction affecting the lung. A type III disease affecting the lung is hypersensitivity pneumonitis and an important type IV hypersensitivity disease affecting the lung is tuberculosis.

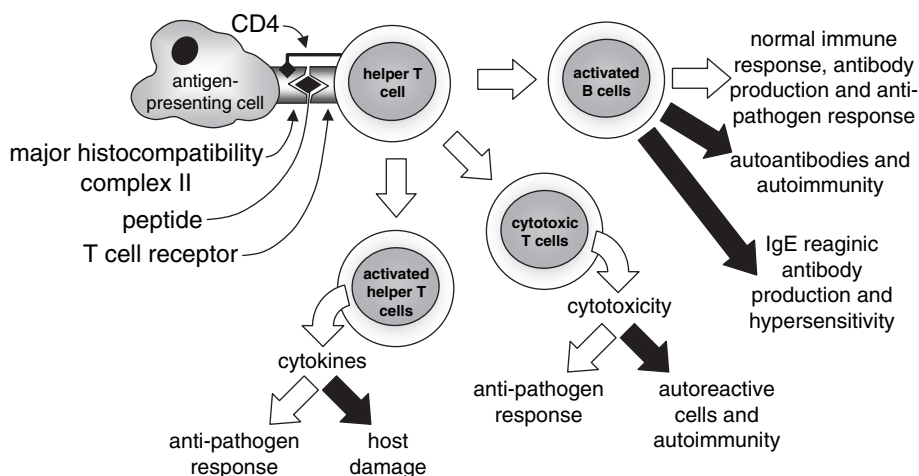


Figure 1.3 Appropriate (open arrows) and inappropriate (closed arrows) immune responses

Trigger box Hypersensitivity reactions

Type I

IgE.

Primary and secondary mediators from mast cells, basophils.

Asthma, allergic rhinitis, eczema, urticaria, food allergies, systemic anaphylaxis.

Type II

Cytotoxic.

IgG against cell surface antigens – complement-mediated damage.

Blood group incompatibilities in transfusion, autoimmune haemolytic anaemia (AHA), erythroblastosis fetalis, Goodpasture's syndrome.

Type III

Antigen/antibody (Ag/Ab) complexes – complement activation, neutrophil infiltration.

Arthus reaction, serum sickness, vasculitis, glomerulonephritis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), hypersensitivity pneumonitis.

Type IV

Cell mediated.

Th1 cells release cytokines – macrophage, T-cell activation – tissue damage.

Contact dermatitis, TB.

Trigger box Tuberculosis

Primary TB – usually lung; usually asymptomatic.

Reactivation leads to post-primary TB (most cases of symptomatic TB), miliary TB.

Findings: Ghon complex (caseating lesions in lymph nodes + granuloma).

Kidney most common site of extrapulmonary TB.

Features: Malaise, anorexia, weight loss, fever, cough, haemoptysis, mucoid, purulent sputum.

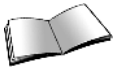
Investigations: CXR, ZN stain, Lowenstein–Jensen culture, Mantoux test.

Mantoux positive 5–15 mm in 48–72 h indicates infection and/or bacille Calmette–Guérin (BCG) vaccination.

BCG reduces TB development by 50%.

Treatment: Rifampicin, isoniazid (INH), pyrazinamide, ethambutol.

Pyridoxine to reduce INH neurotoxicity.



List common allergens



Can you list the main pathogens responsible for 'colds'?

Trigger box Hypersensitivity pneumonitis

A type III hypersensitivity reaction secondary to inhaled organic material (e.g. mouldy hay spores).

Examples: Farmers' lung, bird fanciers' lung.

Findings: Thick alveolar walls, granulomas with histiocytes and plasma cells. Fibrosis in chronic.

Examination: Bilateral crackles.

Diagnosis: CT, lung biopsy.

Treatment: Antigen avoidance, steroids, immunosuppressants.



What are pneumoconioses?

Figure 1.4 shows the mechanism of type I hypersensitivity that is responsible for the pathology of Zoe's acute allergic asthma attack. Note that antigen-binding to IgE stimulates mast cells to release pre-synthesized primary mediators. Synthesis and subsequent release of secondary mediators involve the activation of arachidonic acid and the synthesis and release of prostaglandins and thromboxanes through

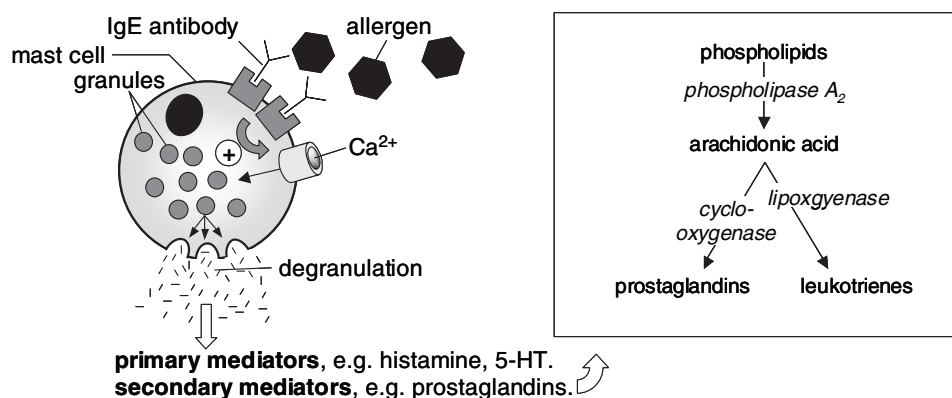


Figure 1.4 Type 1 hypersensitivity*

Table 1.1 Key primary mediators and their effects

Mediator	Characteristics and effects
Histamine	Basic amine stored in granules of mast cells and basophils. Contracts non-vascular smooth muscle, vasodilatation, increased vascular permeability, enhanced mucus secretion, prostaglandin secretion in the lung, chemokinesis
Serotonin	Increased vascular permeability, smooth muscle contraction
ECF A	Eosinophil chemotaxis
NCF-A	Neutrophil chemotaxis

cyclooxygenase pathway and leukotrienes C4 and D4 (termed slow reacting substance of anaphylaxis (SRS-A)) through the lipoxygenase pathway.



What is anaphylaxis? Can you describe the mechanisms underlying systemic anaphylaxis? How is this condition treated?

At the time of her diagnosis, Zoe had been given a skin prick test to confirm her allergic status. She was inoculated with a series of allergens including grass pollen and dust mite extracts. She got a classic wheal and flare reaction after 20 minutes but was surprised when the reaction reappeared around 5 hours later. Immediate reactions occur within minutes of allergen exposure and are mediated principally by the mast cell granule contents (primary mediators). Some 5–8 hours after the immediate reaction has subsided, a second reaction – the late-phase reaction – occurs due to the release of additional secondary mediators including cytokines. Tables 1.1 and 1.2 show the key

*Note that cross-linking of IgE by allergen leads to receptor cross-linkage. This leads to a transient elevation of cAMP, activation of protein tyrosine kinases, methylation of membrane phospholipids and an influx of calcium which causes fusion of granules with plasma membrane and release of primary mediators into extracellular environment. Secondary mediators are synthesized.

Table 1.2 Key secondary mediators and their effects

Mediator	Characteristics and effects
Cytokines	Stimulate and amplify Th2 cell responses (IL-4, IL-13), promote eosinophil production and activation (IL-3, IL-5, GM-CSF) and promote inflammation (TNF- α).
Prostaglandin E ₂	Causes vasodilatation and potentiates increased vascular permeability produced by histamine.
Leukotrienes C ₄ and D ₄	Causes smooth muscle contraction, increased vascular permeability and mucus secretion.
Platelet-activating factor	Synthesized from phospholipid. Causes platelet and neutrophil activation, increased vascular permeability and smooth muscle contraction.
Major basic protein and eosinophil peroxidase	Triggers histamine release from mast cells. Tissue damage.
Bradykinin	Nonapeptide formed from kininogen. Causes vasodilatation, increased vascular permeability and stimulation of pain nerve endings.

Th2, T helper 2; IL, interleukin; GM-CSF, granulocyte-macrophage colony-stimulating factor; TNF- α , tumour necrosis factor- α .

primary and secondary mediators that lead to the inflammatory reaction seen in type I hypersensitivity.

Cytokines are small proteins (5–20 kDa) that are released from cells and act in a similar way as hormones, affecting cellular behaviour. Cytokines allow cells of the immune system to communicate with each other to modulate immune responses. Cytokines are important in mediating many different types of immune responses. Table 1.3 shows the functions of some key cytokines.

Table 1.3 Some key cytokines and their function

Cytokine	Function
IL-1	Stimulates T- and B-cell proliferation and is a pyrogen
IL-2	Stimulates T- and B-cell proliferation and activates natural killer cells
IL-3	Stimulates B memory cells
IL-4	Stimulates plasma cell formation, IgE synthesis and activates B cells
IL-5	Stimulates plasma cell secretion of IgA and IgM, stimulates B cells and eosinophils
IL-6	Induces B-cell differentiation into plasma cells and induces T-cell proliferation and activation
IFN- α	Inhibits viral replication
IFN- β	Inhibits viral replication
IFN- γ	Stimulates monocytes and macrophages and decreases viral replication
TNF- α	Cytotoxic to tumour cells, cachexia
TNF- β	Cytotoxic and increase phagocytosis



Describe the following terms as applied to cytokine action:

Autocrine
Paracrine
Endocrine
Redundancy
Antagonism
Pleiotrophy
Synergy.

What are the four signs of inflammation?

Which cells are found in sites of acute and chronic inflammation?

Can you define the following: triggers, inducers, intrinsic and extrinsic asthma.

The 'blue' inhaler didn't seem to work for Zoe and she knew what this meant. She was heading for another major asthma attack. Zoe called out to Mary around 7pm. Mary heard her and raced upstairs to find Zoe breathing rapidly, gasping for breath and wheezing. She was sitting at her desk, all hunched up; she could barely speak.

What is the normal respiratory rate for young adults?

Mary called out to John who took one look at Zoe and decided to take her to the Emergency Doctor. Since both John and Mary had been drinking, they had to call a taxi! Zoe was breathing with great difficulty. This distressing scene leads us to consider the mechanics of breathing shown in Figure 1.5.

Note that during inspiration as the chest wall expands (external intercostals) and the diaphragm moves down the two pleurae are moved apart. This causes a more negative

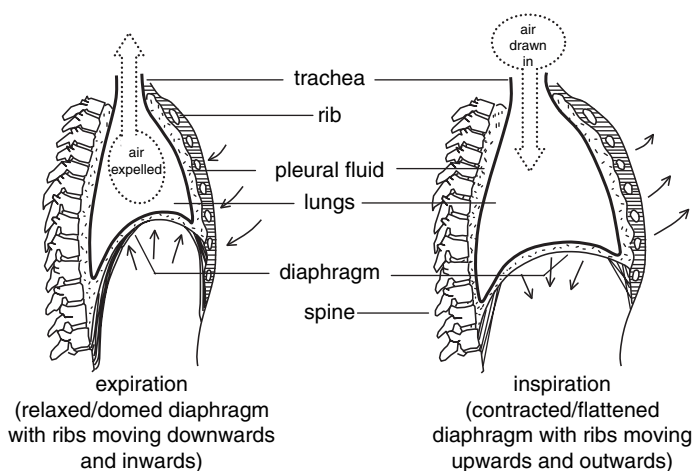


Figure 1.5 The mechanism of breathing. Adapted from Mackean (1969), Introduction to Biology, 4th edition, John Murray, London, p.101.

intrapleural pressure (subatmospheric) to develop. This increase in negative intrapleural pressure overcomes the natural elasticity (elastic recoil) of the lungs and the surface tension of the inner alveoli lining and the lungs inflate, the negative alveolar pressure drawing air into the lungs. Intercostal nerves innervate the intercostal muscles and the diaphragm is innervated by the phrenic nerve (C3, C4, C5).

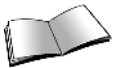


Why is a head injury that causes damage to spinal cord above C3, C4 or C5 potentially fatal?

The accessory muscles, scaleni, sternocleidomastoids and pectoralis are used in forced inspiration. Remember how Zoe is sitting during her acute asthma attack – she is utilizing her accessory muscles.

The diaphragm is the most important structure involved in breathing. In severe asthmatics, airway obstruction causes air trapping, which tends to hyperinflate the lungs. This causes a barrel-shaped thoracic cavity and a flattening of the diaphragm, which impairs its movement during breathing and leads to shortness of breath.

Some years later Max, Debbie's boyfriend was rushed into the ED after being stabbed in the chest. His left lung collapsed because air was getting into the pleural cavity and was unable to leave because his shirt was stuck to his chest. This is called a tension pneumothorax and a chest tube had to be inserted to remove the trapped air and reinflate his lung.



Describe other types of pneumothorax.
Define atelectasis.

Let us now consider the important lung feature of compliance. Compliance is a measure of how expandable the lungs are for a given change in pressure. Zoe's lung compliance is nearly normal. On the other hand Ted, Grandma Irene's brother living down the street who suffers from emphysema has an increased lung compliance. Figure 1.6 shows compliance in different conditions and how compliance can be calculated.

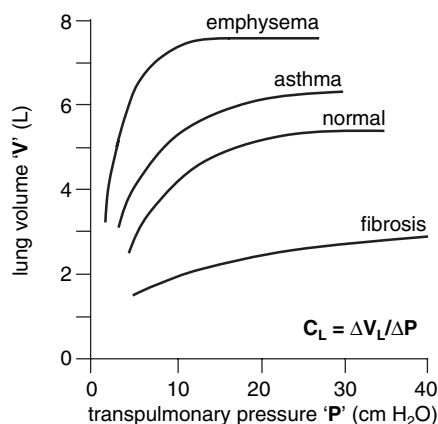


Figure 1.6 Compliance. Adapted from Berne and Levy (1996) Principles of Physiology, 3rd edition, Mosby

***Why does kyphoscoliosis reduce compliance?***

The Emergency Doctor listened to Zoe's lungs; she was very wheezy. Zoe's pulse was also checked, which was found to be 109 beats/minute (bpm). Her blood oxygen saturation (O_2 sats) was 78 per cent. Zoe was given nebulized salbutamol. After 5 minutes Zoe was able to talk in complete sentences. Her wheezing was less noticeable and her O_2 sats had gone up to 95 per cent.

***What caused the wheezing?******What is the normal oxygen saturation in arterial blood?******Why was Zoe tachycardic?******What is pulsus paradoxus?***

On the following Tuesday Mary took a rather reluctant Zoe to see Dr Smith their family doctor. Zoe didn't understand why she had to go, as she was feeling fine. Mary disagreed: Zoe's asthma appeared to be worsening.

Dr Smith asked about her allergies and Zoe mentioned that her asthma was worse after dusting and that she suffered with hay fever in the summer. Zoe also mentioned that her asthma was worse at night and that she would cough and sometimes get wheezy.

Exercise, especially in the cold also made it worse. Zoe then added that she had been suffering from a bad cold 3 days prior to the last big attack.

Dr Smith carried out a full respiratory examination and found Zoe to be tachypnoeic, with a respiration rate of 26 breaths/min and a pulse of 92 bpm. Zoe's ability to expand her chest was checked and found to be normal, but percussion revealed a hyper-resonance and auscultation, some minor wheezing.

Dr Smith then carried out three peak flow readings, which revealed a best of 420 L/min. He reviewed Zoe's file and noted that a spirometry examination carried out 6 months ago had indicated a FEV_1 of 2.4 L and a FEV_1/FVC ratio of 61%. (Figure 1.7 shows the important lung volumes and capacities, and the legend defines the terms commonly used.)

***How do you carry out a peak flow test?***

At the surgery Zoe showed a peak expiratory flow rate (PEFR) of 420. PEFR is the maximum flow achieved in one forced expiration. PEFR is a useful clinical tool to assess the degree of airway obstruction, particularly in asthma.



List the key conditions that lead to a decrease of peak flow.

Dr Smith also noted an eosinophilia in a routine blood test carried out around 6 months ago. A chest X-ray performed at the time also indicated moderate hyperinflation.

***What is the role of the eosinophil in asthma?***

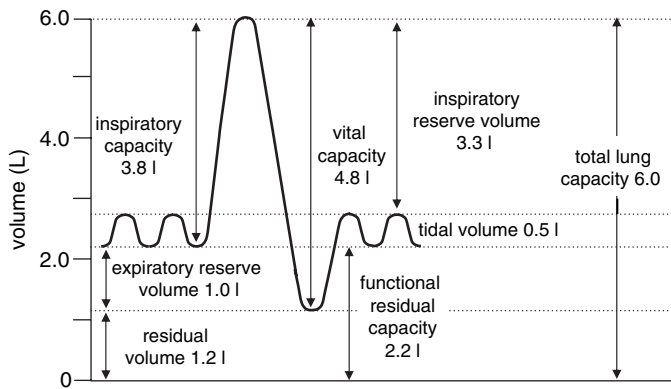


Figure 1.7 Lung volumes and capacities

Lung volumes

Tidal volume, TV: Volume of a single breath, usually at rest.

Inspiratory reserve volume, IRV: Volume that can be inspired beyond a restful inspiration.

Expiratory reserve volume, ERV: Volume that can be expired beyond a restful expiration.

Residual volume, RV: Volume remaining in the lungs after a maximum expiration. This volume keeps the alveoli inflated.

FEV₁ is the volume of gas expelled in first second.

Lung capacities

Total lung capacity: Sum of all the respiratory volumes and residual volume.

$$TLC = FRC + IC = VC + RV$$

Vital capacity, VC: The vital capacity is the maximum volume, which can be ventilated, in a single breath. $VC = IRV + TV + ERV$. VC varies with gender, age, and build. Measuring VC helps to diagnose respiratory disorders, and is a benchmark for judging the effectiveness of treatment.

Functional residual capacity, FRC: Volume of gas left in the lungs at end of quiet expiration.

Inspiratory capacity: Tidal volume plus inspiratory reserve volume.

Forced vital capacity, FVC: Total volume of expired gas, similar to vital capacity but measured during forced expiration.

Dr Smith then reviewed Zoe's medication. She was on the 'brown' inhaler and was also advised to use the 'blue' inhaler when required. She was also on oral steroids. So, let us now look at the drugs Zoe is using. Table 1.4 shows the main drugs used in asthma.



Why would you have to be careful about prescribing (a) aspirin and (b) beta blockers to asthmatic patients?

What are the main side effects of chronic corticosteroid use?



Describe the Step 1–4 treatment strategies in asthma.

Table 1.4 The main drugs used in asthma

Beta agonists	Salbutamol, albuterol, salmeterol (long acting). They relax airway smooth muscles (via β_2 adrenoceptors). Adverse effect: tachycardia (via β_1 adrenoceptors).
Corticosteroids	Beclomethasone, prednisolone. They prevent production of leukotrienes from arachidonic acid by blocking phospholipase A2. Drug of choice in status asthmaticus
Antileukotrienes	Zileuton – blocks synthesis of lipoxygenase Zafirlukast – blocks leukotriene receptors
Methylxanthines	Theophylline – bronchodilation by inhibiting phosphodiesterase involved in degrading cAMP
Muscarinic antagonists	Ipratropium – blocks muscarinic receptors preventing bronchoconstriction
Cromolyn (cromoglycate)	Prevents release of mediators from mast cells. Effective only as prophylactic
Anti IgE-monoclonal antibody	Neutralizes IgE

Grandma's bad chest...

With the Christmas and New Year holidays over, the Sickalotts returned to their usual routines. Zoe's wheezing was much less pronounced. Things however took a turn for the worse in the bungalow down the road.

Grandma Irene suffered from chronic obstructive pulmonary disease (COPD) and was under the care of Dr Blunt at Hope Hospital. Dr Blunt was also looking after Ted, Irene's brother who was also suffering from COPD. For the last few months Grandma Irene was finding it harder and harder to breathe. But not being one to complain, she had carried on with her routines, which mainly centred on looking after Albert. However, her cough was getting worse and she became breathless on minimal exertion. During Mary's daily visit, on the 8th of January, Albert told Mary that Irene's coughing was getting a lot worse and that she might have a raised temperature. Mary wanted to take Irene to see Dr Smith. Irene declined, stating that she always got like this in the winter. It was no big deal.

Around midnight that same day, John and Mary were woken up by the telephone ringing incessantly. On the other end of the line was a rather shaky Albert saying that Irene had taken a turn for the worse.

John and Mary rushed over to the bungalow. Irene was sitting in her chair in the living room, attached to her oxygen, with Albert standing next to her and looking very distressed. John called an ambulance and the paramedics arrived 10 minutes later. They found Irene gasping for breath. She looked cyanotic and was using her accessory muscles for breathing. Irene was given nebulized salbutamol and taken to hospital.

At the hospital Irene was examined by one of the duty doctors. He noted the mild cyanosis, the jugular venous distension (JVD) and end expiratory wheezing. He also noted high-pitched bronchial sounds on the left side, crackles and dullness to percussion. Irene's chest showed moderate hyperinflation and her nicotine-stained fingers were noted to be clubbed. Her respiration rate was 45 bpm, her BP was 160/95 and she had a temperature of 39°C. Irene was responsive only to repeated verbal commands. Her treatment started with nebulized salbutamol, i.v. steroids and i.v. ampicillin.

What is JVD?

What is the most likely cause of Irene's increased temperature?

What is the significance of dullness to percussion, high pitched bronchial sounds and finger clubbing?

What is the significance of mentioning Irene's nicotine stained fingers?

Why was Irene treated with ampicillin? What is the mechanism of action of ampicillin?

The duty doctor ordered some arterial blood gases (ABGs), which indicated hypoxaemia, hypercapnia (hypercarbia) and mild respiratory acidosis. A chest X-ray was also ordered.

You should be able to explain the mechanisms involved in respiratory acidosis and alkalosis. Respiratory acidosis is seen when arterial PaCO_2 rises above normal (e.g. in Irene's COPD when ventilation was impaired). Conversely, overbreathing, such as during Zoe's acute asthma attack, can cause more CO_2 to be blown off, giving rise to a respiratory alkalosis. Table 1.5 shows the causes of respiratory and metabolic acidosis and alkalosis and also shows the compensatory reactions.

Table 1.5 Acidosis and alkalosis

Condition	Causes	Compensatory mechanism
Respiratory acidosis	Increased PaCO_2 and decreased pH due to hypoventilation caused by any lung, neuromuscular or physical cause of respiratory failure.	Increased renal excretion of H^+ ions and increased reabsorption of HCO_3^- ions.
Respiratory alkalosis	Decreased PaCO_2 and increased pH due to hyperventilation.	Decreased renal excretion of H^+ ions and decreased reabsorption of HCO_3^- ions.
Metabolic acidosis	Decreased HCO_3^- ion concentration and decreased pH caused by excessive HCO_3^- ion loss or increased H^+ production.	Hyperventilation to increase CO_2 excretion and reduce carbonic acid concentration.
Metabolic alkalosis	Increased HCO_3^- ion concentration and increased pH caused by excessive H^+ ion loss.	Hypoventilation to reduce CO_2 excretion and increase carbonic acid concentration.



What are the typical arterial blood gas findings in (a) acute asthma and (b) acute COPD?



List other causes that lead to respiratory acidosis and alkalosis.

By next morning, Irene was much better. The doctor noted her sputum pot and requested a sputum culture. He also requested lung function tests which revealed a FEV₁ of 1.1 L and a FEV₁/FVC ratio of 43 per cent.

Irene, Ted and Zoe suffer from obstructive lung diseases. In these diseases the FEV₁/FVC ratio is <80 per cent, in contrast to restrictive diseases where the ratio is >80 per cent.

Trigger box Key obstructive and restrictive lung diseases

1. Obstructive lung diseases

(FEV₁/FVC <80%; increased TLC; increased FRC; increased RV).

Chronic bronchitis.

Emphysema.

Asthma.

Bronchiectasis.

2. Restrictive lung diseases

(FEV₁/FVC >80%; decreased VC; decreased TLC).

Sarcoidosis.

Diffuse interstitial pulmonary fibrosis.

Scoliosis.

Neuromuscular disease (e.g. polio).

Myasthenia gravis.

Trigger box Diffuse interstitial pulmonary fibrosis

Most common restrictive lung disease.

More common in the elderly.

Pathology: Thick alveolar walls – cystic spaces.

Findings: Shallow rapid breathing, cough.

Reticular pattern/honeycomb pattern on CXR (in severe disease).

Treatment: Supportive, steroids.

What is the aetiology of this disease?

Trigger box Sarcoidosis

Cause unknown.

Multisystemic disease, most common extrapulmonary manifestations: skin/ocular abnormalities.

Female > male, Afro-Caribbeans > Caucasians, 20–40s,

Findings: Restrictive lung disease; erythema nodosum; lupus pernio; hypercalcaemia; uveitis; uviparotid fever; arhythmias; cardiomyopathy; cranial nerve palsies; arthralgias; granulomas (non-caseating); cell-mediated immune depression.

Investigations: CXR (bilateral hilar adenopathy), transbronchial biopsy, angiotensin-converting enzyme (ACE) (increased with disease activity/responds to treatment).

Treatment: Steroids, immunosuppressants.

Trigger box Cystic fibrosis (CF)

Autosomal recessive (AR).

1:2000.

Mutations in *CFTR* – main delta F508.

Defective Cl^- channel.

Features: Viscous secretions – bronchiectasis, obstructive lung disease; meconium ileus; diabetes mellitus.

Pseudomonas aeruginosa infection seen.

Median survival 40 years.

Investigations: Sweat test, genetic screening.

Treatment: Chest physiotherapy, bronchodilators, i.v. antibiotics for exacerbations, DNA'ase, pancreatic enzyme supplements.

Patients suffering from CF can develop bronchiectasis.

Trigger box Bronchiectasis

Permanent bronchial dilatation.

CF most common cause, also idiopathic, postinfective (measles, pneumonia, pertussis), ciliary disorders.

Findings: Cough, sputum, haemoptysis, clubbing, crackles, wheezing.

Investigations: High resolution CT, sputum culture.

Treatment: Physiotherapy, antibiotics, bronchodilators, steroids.

Table 1.6 Age of patient and the pathogens causing pneumonia

Age	Pathogens
Neonates	Group B streptococcus, <i>E. coli</i> .
Children	Respiratory syncytial virus, <i>Mycoplasma pneumoniae</i> , <i>Chlamydia pneumoniae</i> , <i>Streptococcus pneumoniae</i>
Young adults	<i>Mycoplasma pneumoniae</i>
Older adults & elderly	<i>Streptococcus pneumoniae</i>

Irene's chest X-ray showed left lower lobe consolidation suggesting lobar pneumonia. This was confirmed by the sputum culture, which revealed *Streptococcus pneumoniae*. So, Irene was suffering from a chest infection with underlying COPD.

People like Irene who suffer from COPD also suffer from frequent pulmonary infections like pneumonia. The pathogens causing pneumonia depend on the age of the patient, as shown in Table 1.6.

Trigger box **Pneumonia**

Inflammation of lung tissue.

Findings: Pyrexia, cough, sputum, pleurisy, dyspnoea, consolidation, pleural rub, pleural effusion, confusion (elderly).

Blood cultures positive in 20% cases even if sputum is negative: indicates poor prognosis.

Risk factors: Smoking, alcoholism, lung disease, immunosuppression, chronic disease.

Investigations: CXR, FBC (WBC $> 15 \times 10^9/L$ suggests bacterial infection), cold agglutinins in *Mycoplasma pneumoniae*, raised urea and hypoalbuminemia = severe pneumonia, arterial blood gases (ABG) ($PaO_2 < 8 \text{ kPa}$ /hypercarbia = severe pneumonia).

Main pathogens

1. Community acquired: *Streptococcus pneumoniae* (70%). *Mycoplasma pneumoniae*. (15%), *Chlamydia* spp. (7%).
2. Hospital acquired: Gram-negative bacteria (50%).

Treatment:

Community acquired – amoxicillin.

Penicillin allergies – erythromycin or azithromycin.

Staphylococcus aureus – flucloxacillin.

Physiotherapy.

Complications: Lung abscess, empyema.

Mortality 25% in elderly.

Irene has chronic bronchitis, her brother Ted has emphysema. These diseases are part of a group of conditions (together with chronic asthma) that make up COPD. Most COPD sufferers are smokers.

Trigger box COPD

Decreased FEV₁; decreased FEV₁/FVC; increased TLC; increased RV.

Chronic bronchitis/emphysema.

Most are smokers.

Chronic bronchitis (blue bloater):

Features: Productive cough >3/12 for 2 consecutive years, hypercarbia, hypoxia, hyperinflated lungs.

Emphysema (pink puffer):

Centriolobular (smoking); panlobular (α_1 antitrypsin deficiency).

Features: Dyspnoea, decreased breath sounds, hypercarbia, hypoxia, bullae.

Treatment: O₂, beta agonists, ipratropium, steroids, antibiotics.



Can you describe the significance of α_1 -antitrypsin to emphysema?



Smokers are also at a high risk of developing lung cancer. Study the Trigger Box on lung cancer.

Trigger box Lung cancer

Most common malignant tumour.

Types:

1. *Non small cell* (70–80%)

Squamous cell carcinoma (40%), large cell carcinoma (25%) adenocarcinoma (10%).

2. *Small cell* (20–30%).

Causes: Smoking, asbestos.

Features: Cough, chest pain, hemoptysis, finger clubbing, Pancoast's tumour, Horner's syndrome, superior vena cava (SVC) obstruction.

Investigations: CXR, sputum cytology, bronchoscopy, CT, MRI (for Pancoast's tumour)

Treatment: Non small cell – surgery, radiotherapy or chemotherapy. Small cell – chemotherapy \pm radiotherapy.

Irene could develop cyanosis and become a 'blue bloater'. Ted uses his accessory muscles and gets exhausted. He is thin, has a barrel chest and his lungs are fast losing their elasticity and shows high compliance. He has heard Dr Blunt referring to him as a pink puffer.

Let us return to Irene in hospital. The doctor sat next to her and began advising her against smoking when Irene interrupted him politely. She had given up smoking.

'I know all about how bad smoking can be,' said Irene. 'I know . . . look what it did to poor Ted. He's got emphysema you know'.

Patients with COPD without hypercarbia can be treated with 100 per cent O₂ through a facemask. This improves alveolar ventilation. Since the ventilation/perfusion ratio has to be matched arterioles supplying these alveoli dilate so as to increase perfusion. For gas exchange to be efficient there must be match between ventilation and perfusion. You need to know about ventilation and perfusion (Figure 1.8).

Trigger box Pulmonary embolism (PE)

Usually due to a deep venous thrombosis (DVT); how does a DVT cause a PE?
V/Q mismatch

Findings: dyspnoea, pleuritic chest pain, haemoptysis, or if severe shock, syncope and death.

Central cyanosis, elevated JVP (jugular venous pressure), right ventricular (RV) heave, loud heart sound (HS) 2, gallop rhythm

Investigations: VQ scan, D dimers, Doppler US, CT, pulmonary angiogram

Treatment: Oxygen, streptokinase, morphine, i.v. heparin/warfarin for prevention, i.v. fluids, inotropes, vena caval filter.



What is the key difference between systemic capillaries and pulmonary capillaries in terms of their response when flowing through hypoxic regions?

Uncle Ted came to visit Irene in hospital. He looked a bit perturbed. He mentioned a conversation he had overheard between Dr Blunt and a medical student, where his increased dead space had been discussed. Dead space refers to the volume that is ventilated but does not participate in gas exchange. Anatomical dead space includes all the conduit airways down to bronchioles. Since Ted has air in his conduction system

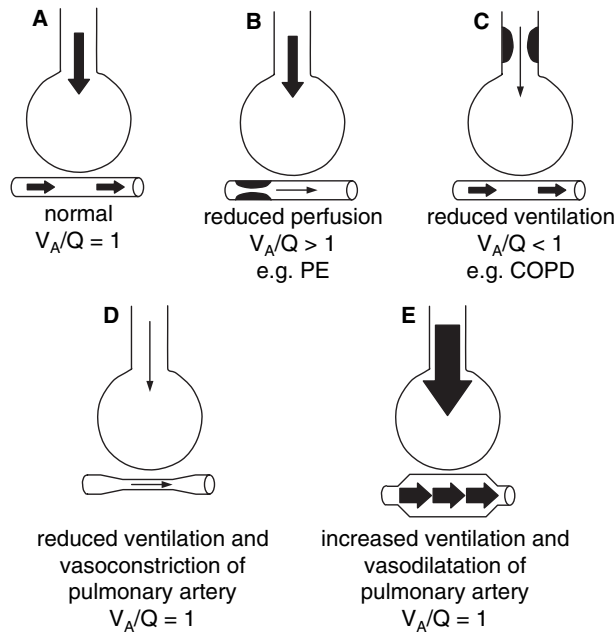


Figure 1.8 Ventilation and perfusion. 'D' and 'E' shows how vasodilatation or vasoconstriction corrects a V_A/Q mismatch

The V/Q ratio = alveolar ventilation rate/pulmonary blood flow

If there is no ventilation, $V_A/Q = 0$

For example you get perfusion without ventilation when an alveolus is full of liquid as in severe pneumonia. This will reduce arterial PaO_2 .

If there is no perfusion, $V_A/Q = \infty$

Here the alveoli are ventilated but not perfused, for example due to a pulmonary embolus.

Remember pulmonary vessels constrict in poorly ventilated regions.

A pulmonary embolus is a medical emergency and causes a severe V/Q mismatch.

and lots of destroyed alveoli, which do not participate in gas exchange, he has lots of dead space! Physiological dead space includes alveoli that are ventilated but not perfused, which occurs in patients suffering with pulmonary emboli.

Note: alveolar ventilation rate = (tidal vol – dead space) \times respiratory rate



Dead space is increased in artificial respiration when the patient is connected to tubing. What physiological effects will this have on the patient's tidal volume and respiratory rate?

After talking about dead space, Dr Blunt had gone on to describe things that caused Ted to experience even more fear.

'The loss of functional alveoli in emphysema,' he had said, 'will reduce diffusion capacity and therefore impair gas exchange. You can also see this in pulmonary oedema.'

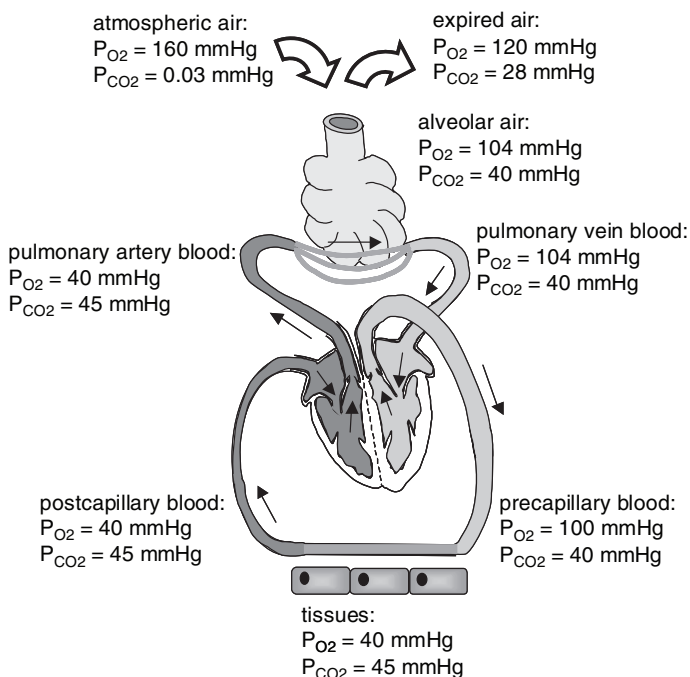


Figure 1.9 Gas exchange. Adapted from Sherwood (2004) Human Physiology from Cells to System, 5th edition, Thomson, Brooks/Cole.

Figure 1.9 shows changes in P_{aO_2} and P_{aCO_2} as blood moves from metabolically active tissues to the lungs and back.

?

What drives the movement of these gases from tissue to venous blood, from venous blood to alveoli, from alveoli to arterial blood and from arterial blood to tissue?

Why is P_{aO_2} in systemic arterial blood lower than that in pulmonary veins?

Which hormone increases RBC formation? Where is it produced?



List the causes of pulmonary oedema.

?

How is diffusion capacity measured?

What conditions reduce diffusion capacity?

Zoe's oxygen saturation at the height of her asthma attack was 78 per cent. After treatment it rose to 98 per cent. You need to know about haemoglobin (Hb) and O_2 saturation curves. O_2 carrying capacity of the blood is proportional to the Hb concentration in the alveoli. Hb has four O_2 binding sites. The shape of the dissociation curve is

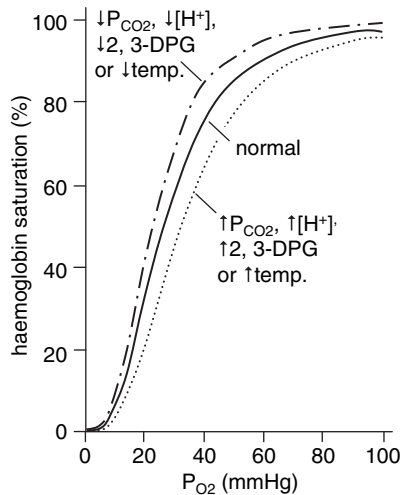


Figure 1.10 Oxygen dissociation curves (also shows the Bohr effect). Adapted from McGeown (1999) Physiology, Churchill Livingstone

due to the fact that binding of one Hb molecule increases the binding capacity of other sites. Factors, which shift the O_2 dissociation curve, are shown in Figure 1.10.

The physiological significance of these shifts is seen when it is appreciated that all factors that shift the curve to the right are seen in systemic capillaries where O_2 unloading is the goal.



Can you explain the significance of increased 2-3 diphosphoglycerate (DPG)?

The Bohr effect is seen when the $PaCO_2$ levels are increased. The curve shifts to the right so that the O_2 saturation is lower for a given PaO_2 . Hence the curve for systemic venous blood with higher $PaCO_2$ lies to the right of arterial blood. This increases O_2 extraction as blood flows through actively respiring tissues that generate CO_2 .

Different types of Hb also affect O_2 dissociation curves. Figure 1.11 shows O_2 dissociation curves for fetal Hb and myoglobin.



Describe the significance of the shapes of the dissociation curves of fetal haemoglobin and myoglobin.

Some conditions reduce O_2 affinity of haemoglobin. Example when Fe^{2+} is converted Fe^{3+} to form methaemoglobin which has a reduced O_2 binding capacity.



List the main causes of methaemoglobinaemia.

A few years ago there was a fire two houses down from the Sikalott home. Fortunately no one died but several people had to be taken to hospital with carbon monoxide

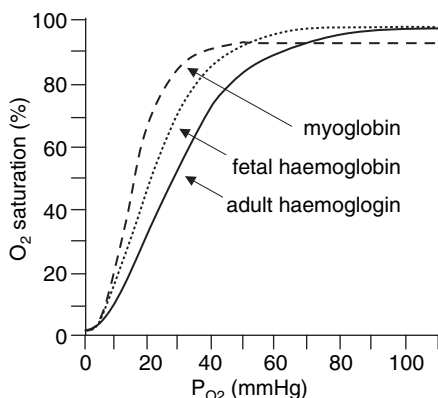


Figure 1.11 Dissociation curves for different oxygen carriers. Adapted from McGeown (1999) Physiology, Churchill Livingstone

poisoning. CO binds with greater affinity to haemoglobin than O_2 and forms carboxyhaemoglobin, as seen in Figure 1.12.



Why do patients suffering from CO poisoning appear a pink - red colour?

Let us now consider CO_2 transport.

CO_2 is transported in three forms:

1. As HCO_3^- (60–70 per cent). (See Figure 1.13)
2. In carbamino groups - mostly binding to Hb (20–30 per cent).
3. As dissolved gas (10 per cent).

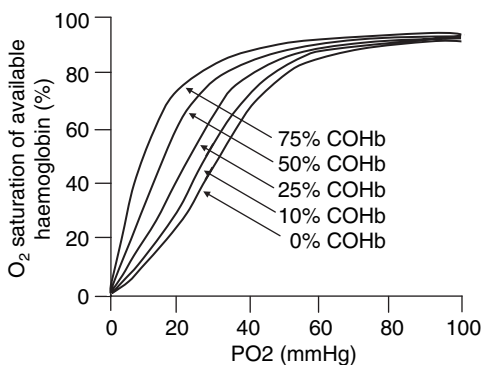


Figure 1.12 The effects of carbon monoxide on the oxygen carrying capacity of blood. Adapted from www.coheadquarters.com/cohaldane1.htm

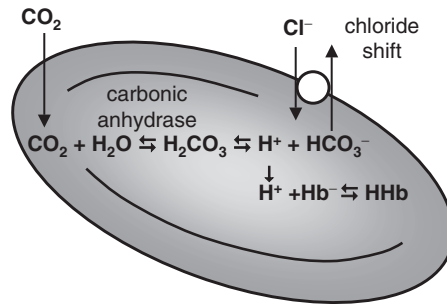


Figure 1.13 Carbon dioxide metabolism in the erythrocyte. Adapted from Ganong (1991) Review of Medical Physiology, 15th edition, Appleton & Lange



What is the chloride shift

CO₂ dissociation curves (not shown) show higher CO₂ concentrations at a given PaCO₂ when compared to the situation in the O₂ dissociation curve. This is because CO₂ is more soluble. Also when comparing to the O₂ dissociation curve, CO₂ has a narrower physiological range and no plateau.

The Haldane effect describes how the CO₂ dissociation curve shifts down and to the left when the PaO₂ is increased. Hence the CO₂ concentration drops at a given PaCO₂. The Haldane effect increases the uptake of CO₂ from respiring tissues. The Haldane effect is due to deoxygenated Hb being able to carry more CO₂ in the carbamino form and because it is a more effective pH buffer than oxyhaemoglobin. The Haldane effect is shown in Figure 1.14.

Whilst in hospital Ted found out that someone in the next room was having an even tougher time. He overheard Dr Blunt explaining- to his student – that “this fellow was

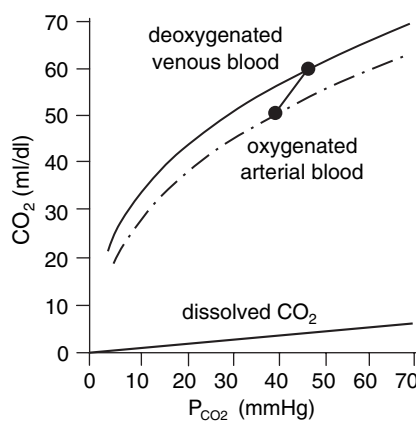


Figure 1.14 The Haldane effect. Adapted from McGeown (1999) Physiology, Churchill Livingstone

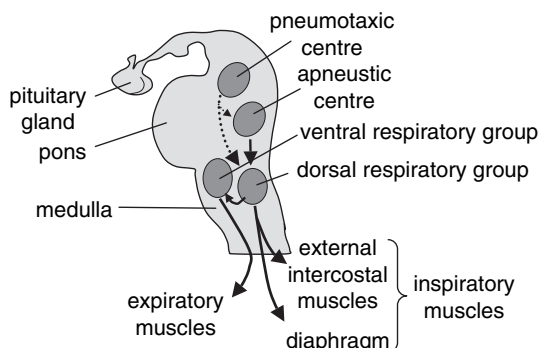


Figure 1.15 Respiratory centres showing stimulatory (solid arrows) and inhibitory (dotted arrows) pathway connections. Adapted from Tortora and Grabowski (2003), *Principles of Anatomy and Physiology*, 10th edition, John Wiley & Sons

showing apneustic breathing – long inspiratory breaths followed by brief exhalations”. Dr Blunt explained that “breathing was regulated by the brain stem” and that “this fellow had had a stroke that had caused damage to his pons” – whatever that is! This brings us to the control of respiration, which is shown, in Figure 1.15.

Inspiratory respiratory neurones in the medulla (DRG) stimulate motor neurones reaching the diaphragm and external intercostals. These inspiratory respiratory neurones show spontaneous rhythmical activity with pauses, which cause expiration to occur passively.

Expiratory respiratory neurons (VRG) only become active during episodes of increased (forced) ventilation. These stimulate motor neurons causing internal intercostals and abdominal muscles to contract. Respiratory cells in the pons are not essential for respiration but can modify the pattern of breathing. The pontine pneumotaxic centre inhibits inspiratory neurons and shortens inspiration.

You need to understand the central and peripheral chemoreceptor control of respiration shown in Figure 1.16.

Increases in arterial PaCO_2 increase ventilation by stimulating central chemoreceptors in the medulla. Chemoreceptor cells are actually sensitive to H^+ ions formed by CO_2 crossing the blood–brain barrier and reacting with water:



An arterial acidosis however has little immediate effect on central chemoreceptors because H^+ ions cannot cross the blood–brain barrier.

In contrast PaO_2 stimulate central chemoreceptors less well. However if PaO_2 drops a lot it can stimulate ventilation by activating peripheral chemoreceptors. Peripheral chemoreceptors (carotid and aortic bodies) respond to increased arterial pH and low PaO_2 . Hypoxia of an adequate degree will therefore stimulate ventilation via peripheral chemoreceptors.

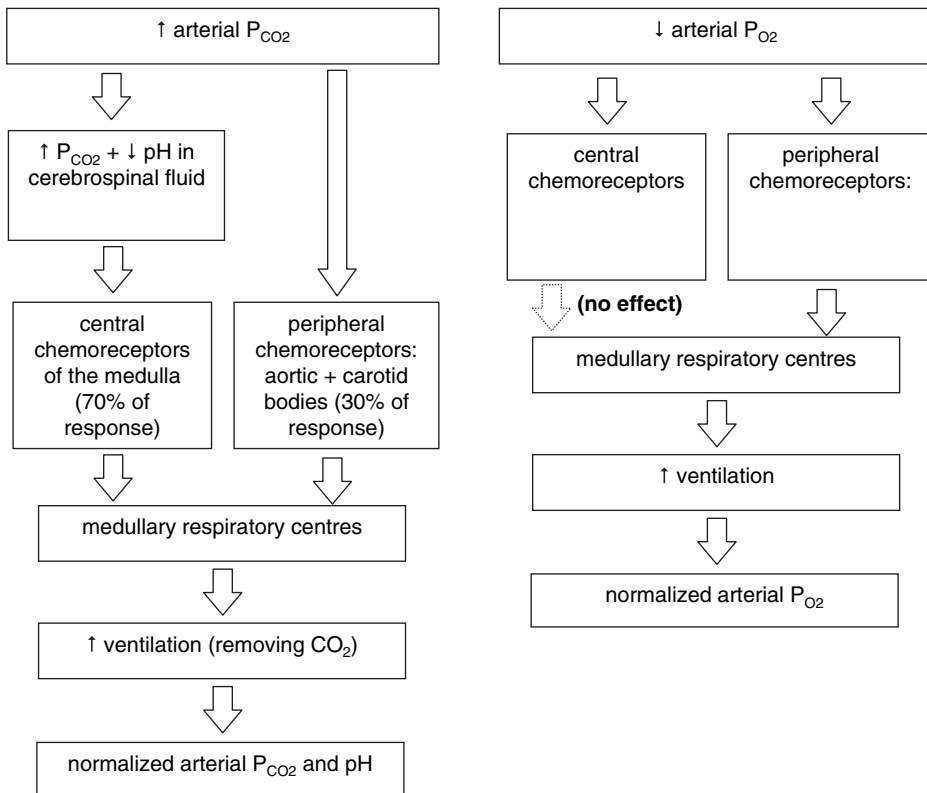


Figure 1.16 Central and peripheral chemoreceptor control of breathing

Irene has hypoxic drive because her PaCO₂ is chronically elevated due to her COPD. Her central chemoreceptors have become unresponsive and her oxygen sensitive peripheral chemoreceptors now respond to lowered PaO₂.

You have to be careful giving her 100 per cent O₂ because this can remove the stimulus for her breathing.



What happens if the spinal cord is transected just below the pons?

Describe the main changes seen in respiratory physiology in (a) high altitude, (b) vigorous exercise

