

This Special Edition of Update in Anaesthesia was produced with the kind support of the Association of Anaesthetists of Great Britain and Ireland

Update in **Anaesthesia**

Education for anaesthetists worldwide

Volume 24 Number 2

December 2008

Editor-in-chief: Bruce McCormick

ISSN 1353-4882



The Journal of the World Federation of Societies of Anaesthesiologists

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News from the WFSA

Safety and Quality of Practice Committee

The goal of the WFSA is to improve the standard of anaesthesia world-wide. The Safety and Quality of Practice Committee is contributing to this through several projects.

Web Site Development has been an important part of establishing communication with members of WFSA. The site continues to be updated regularly by Safety and Quality of Practice webmaster Dr Nian Chih Hwang. An alerts section has been created.

Standards. The International Standards for Safe Anaesthesia developed by an independent task force, endorsed by the WFSA at the Hague, and published in 1993, have been revised as part of a WHO Global Challenge, Safe Surgery Saves Lives. Many people assisted me with this task, notably Iain Wilson, Meena Cherian, Olaitan Sanyanwo, Jeff Cooper and John Eichhorn (who was part of the original task force). The revised standards were endorsed by the General Assembly of the WFSA in Cape Town. They can be viewed on the website: www.anaesthesiologists.org.

The Executive of the WFSA has also endorsed a standard promoting the interoperability of anaesthesia equipment, and this too can be seen on the website.

The Global Oximetry Project is a collaborative project between WFSA, AAGBI and GE Healthcare, to provide low cost pulse oximeters in a package that includes education, collection of data and agreements with local anaesthesia providers and healthcare administrators to achieve long term sustainable change in practice. The GO Committee was initiated from the Safety and Quality of Practice Committee, with Dr Gavin Thoms as our representative and overall Chair. Sub-projects are underway in Uganda, the Philippines, Vietnam and India. The aim has been for each sub-project to be self-funding. GE Healthcare has donated a total of 58 oximeters, 125 sensors, and training materials and has provided considerable logistical support (hosting teleconferences, delivering the oximeters, providing maintenance etc). GE has proven to be a great partner in this effort and we are grateful for the ongoing support for this important effort. We are particularly grateful for the ongoing commitment of Mark Philips and Colin Hughes.

The participating anaesthesia professionals have completed logbooks, and data was presented at the World Congress in Cape Town. A final report is in preparation, to be followed by peer reviewed publications.

For various reasons, the tripartite structure was wound up in Cape Town, and the GO project returned to the oversight

of the WFSA Safety and Quality of Practice Committee. It remains this Committee's single most important activity, and follow-on visits to Uganda and Vietnam, to nurture the progression of these projects to the goal of "sustainable change in practice" are planned.

WHO, Safe Surgery and Pulse Oximetry: Iain Wilson and I have also been involved in the World Health Organisation Safe Surgery Saves Lives (not as representatives of WFSA) and have been very gratified to see the development of a universally applicable checklist with considerable relevance to the promotion of teamwork in the operating room and support for the importance of anaesthesia in safe surgery. The WHO is now progressing a follow on initiative to advance the GO project. This will build on the work of the WFSA GO project, with the full weight of the WHO to extend this project into its next phase.

The Virtual Anesthesia Machine (an independent educational project under the direction of Dr Sem Lampotang) is supported by the SQPC, and links to this project are in place from our website.

Crisis Management Manual. A link from which a PDF of the Australian Patient Safety Foundation Crisis Management Manual is to be made available through the website. We are very grateful to the APSF for this.

Incident Reporting – Professor Quirino Piacevoli is responsible for a new project to make incident reporting available to countries that do not currently have access to this facility.

Drug safety – efforts to promote clearer, more standardised presentation of information on the labels of drug ampoules will be an activity of increased importance for the SQPC over the next four years.

Liaison with other organisations - these include ANZCA, the RCoA, Operation Smile, and strong links with several member societies, notably AAGBI and NZSA.

Please contact me if you have any comments or suggestions, or would like to contribute to any of this Committee's activities.

Thank you,

Alan Merry

Chair

Safety and Quality of Practice Committee

Editorial

This special edition of *Update in Anaesthesia* focuses exclusively on basic science topics. A proportion of these topics have been covered in previous editions of *Update*, reflecting that a sound knowledge of basic science is the cornerstone of safe and appropriate practice as an anaesthetist. We must, for example, be able to identify the risks of electrical injury or explosions in theatre, avoid inadvertent light anaesthesia or dangerous overdose when using vapours, and understand normal physiology so that we can recognise and treat the physiological abnormalities of critically ill or injured patients, when we are confronted by them. Where resources are stretched, there is a clear need for an anaesthetist to be able to understand, and provide some maintenance for his or her equipment, particularly if the facilities for more formal engineering support are absent or at some distance.

The importance of basic science to our speciality is demonstrated by the prominence of basic science in the curricula produced by anaesthetic training schools around the world; the new year one/two curriculum for the Royal College of Anaesthetists' e-Learning in Anaesthesia program has over one third of its nine hundred learning sessions dedicated to basic science topics. This is reflected in the make up of the college's examinations - in the UK the two Primary FRCA vivas, aimed at assessing an anaesthetists basic anaesthetic training, comprise fifty per cent basic science.

In drawing up a 'wish-list' of core text books appropriate for use by anaesthetists in developing countries, the International Relations Committee of the Association of Anaesthetists of Great Britain and Ireland (AAGBI) identified that no available basic science text dealt specifically with the needs of anaesthetists in developing countries. It was the suggestion of that committee that lead to the conception of this Special Edition, which has been jointly funded by the World Federation of Societies of Anaesthesiologists and the Overseas Anaesthesia Fund of the AAGBI Foundation.

Within the available resources, it is not possible for this edition to be a comprehensive guide to the basic science relevant to anaesthesia. Where possible we have used previously published *Update*

articles or articles published as part of the WFSA's *Anaesthesia Tutorial of the Week* series. Each of these articles has been rigorously edited and adapted to ensure that they are both contemporary and relevant to anaesthetists working in conditions of limited resources. Above all we have tried to emphasise the practical applications of basic science to daily practice as an anaesthetist. Over a quarter of the forty articles within this edition are newly commissioned. The priority to cover as many of the core subjects within physiology, pharmacology and physics as possible, has lead to the omission of other topics, such as anatomy and biochemistry which unfortunately remain poorly covered. I will be very pleased to receive requests for topics that have not been represented within this edition, which will be commissioned and appear in subsequent issues. Please contact me at Bruce.McCormick@rdeft.nhs.uk.

I am greatly indebted to the editorial board of *Update in Anaesthesia* for their hard work and also the editors of *Anaesthesia Tutorial of the Week*, particularly Carl Gwinnutt, who is section editor for Basic Sciences, and a major contributor to this edition. I also thank a large team of local colleagues who have given up their time to help with this project and Dave Wilkinson for his tireless efforts producing figures for many of these articles.

Update in Anaesthesia will soon be available as a free download, as whole editions or individual articles, from the WFSA's website, www.anaesthesiologists.org. The same educational resources section of this website hosts *Anaesthesia Tutorial of the Week*, which continues to build as a freely-available educational library for anaesthetists in all countries of the world.

I hope that this edition proves to be a useful and reliable aid for both qualified and trainee anaesthetists. If you wish to receive the printed version of subsequent editions of *Update* please email Carol Wilson at worldanaesthesia@mac.com. Further copies of this edition are available via TALC (Teaching-aids at Low Cost) at www.talcuk.org

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PHYSIOLOGY

- 6 An Introduction to Cardiovascular Physiology**
James Rogers
- 11 Aspects of Myocardial Physiology**
AM Campbell and JA Hulf
- 15 Respiratory Physiology**
Fred Roberts and Ian Kestin
- 20 The Physiology of Oxygen Delivery**
Rob Law and Henry Bukwirwa
- 26 Carbon Dioxide Transport**
GJ Arthurs and M Sudhakar
- 30 Cerebral Blood Flow and Intracranial Pressure**
Lisa Hill and Carl Gwinnutt
- 36 The Autonomic Nervous System - Basic Anatomy and Physiology**
Oliver Pratt, Carl Gwinnutt and Sarah Bakewell
- 40 The Physiology of Neuromuscular Junction**
Clare Ackroyd
- 43 Body Fluid Compartments, Sodium and Potassium**
Daniel Freshwater-Turner, Richard Green and Bruce McCormick
- 52 Endocrine Physiology**
PA Farling, ME McBrien and D Breslin
- 60 Renal Physiology**
Katie Wallace
- 66 Liver Physiology**
Tasneem Katawala
- 69 Physiology of Pain**
K Venugopal and M Swamy
- 72 Physiological Changes Associated with Pregnancy**
Christopher Ciliberto, Gertie Marx and Darryl Johnston

An Introduction to Cardiovascular Physiology

James Rogers

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INTRODUCTION

The cardiovascular system consists of the heart and two vascular systems, the systemic and pulmonary circulations. The heart pumps blood through these two vascular systems - the low pressure pulmonary circulation in which gas exchange occurs, and then the high pressure systemic circulation, which delivers blood to individual organs, matching supply to metabolic demand. Blood pressure and flow are largely controlled by the autonomic nervous system, and are also influenced by surgery and anaesthetic drugs.

THE HEART

The heart comprises four chambers, and is divided into a right and left side, each with an atrium and a ventricle. The atria act as reservoirs for venous blood, with some pumping action to assist ventricular filling. In contrast, the ventricles are the major pumping chambers, delivering blood to the pulmonary (right ventricle) and systemic (left ventricle) circulations. The left ventricle is conical in shape and has to generate greater pressures than the right ventricle, and so has a much thicker and more muscular wall. Four valves ensure that blood flows only one way, from atria to ventricle (tricuspid and mitral valves), and then to the arterial circulations (pulmonary and aortic valves). The myocardium consists of muscle cells, which can contract spontaneously and pacemaker and conducting cells, which have specialised functions.

ELECTROPHYSIOLOGY OF THE HEART

Myocardial contraction results from a change in voltage across the cell membrane (depolarisation), which leads to an action potential. Although contraction may happen spontaneously, it is normally in response to an electrical impulse. This impulse starts in the sinoatrial (SA) node, a collection of pacemaker cells located at the junction of the right atrium and superior vena cava. These specialised cells depolarise spontaneously, and cause a wave of contraction to pass across the atria. Following atrial contraction, the impulse is delayed at the atrioventricular (AV) node, located in the septal wall of the right atrium. From here His-Purkinje fibres allow rapid conduction of the electrical impulse via right and left branches, causing almost simultaneous depolarisation of both ventricles,

approximately 0.2 seconds after the initial impulse has arisen in the sinoatrial node. Depolarisation of the myocardial cell membrane causes a large increase in the concentration of calcium within the cell, which in turn causes contraction by a temporary binding between two proteins, actin and myosin. The cardiac action potential is much longer than that of skeletal muscle, and during this time the myocardial cell is unresponsive to further excitation (the refractory period).

The electrocardiogram (ECG)

The ECG measures changes in skin electrical voltage/potential caused by electrical currents generated by the myocardium. The P wave reflects atrial depolarisation, the QRS complex ventricular depolarisation, and the T wave ventricular repolarisation. Repolarisation is a process that occurs in many cells where the electrical potential across the cell membrane returns from the value during the action potential to that of the resting state, the resting potential. Although the ECG shows heart rate and rhythm and can indicate myocardial damage, it gives no information on the adequacy of contraction. Normal electrical complexes can exist in the absence of cardiac output, a state known as **pulseless electrical activity**.

CARDIAC OUTPUT

Cardiac output (CO) is the product of heart rate (HR) and stroke volume (SV): $CO = HR \times SV$

For a 70kg man normal values are $HR=70\text{min}^{-1}$ and $SV=70\text{ml}$, giving a cardiac output of about $5\text{L}\cdot\text{min}^{-1}$. The cardiac index is the cardiac output per square metre of body surface area and normal values range from $2.5\text{--}4.0\text{L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$.

Heart rate is determined by the rate of spontaneous depolarisation at the sinoatrial node (see article on myocardial physiology), but can be modified by the autonomic nervous system. The vagus nerve acts on muscarinic receptors to slow the heart, whereas the cardiac sympathetic fibres stimulate beta-adrenergic receptors and increase heart rate.

Stroke volume is determined by three main factors: preload, afterload and contractility.

Summary

This article aims to provide an overview of the physiology of the cardiovascular system and its response to anaesthesia. The next article in this section deals with myocardial physiology in greater detail.

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Preload is the ventricular volume at the end of diastole. An increased preload leads to an increased stroke volume. Preload is mainly dependent on the return of venous blood from the body and is influenced by changes in position, intra-thoracic pressure, blood volume and the balance of constriction and dilatation (tone) in the venous system. The relationship between ventricular end-diastolic volume and stroke volume is known as 'Starling's law', which states that the energy of contraction of the muscle is related/proportional to the initial length of the muscle fibre. This can be graphically illustrated by a series of 'Starling curves' (Figure 1). As volume at the end of diastole (end-diastolic volume) increases and stretches the muscle fibre, so the energy of contraction and stroke volume increase, until a point of over-stretching when stroke volume may actually decrease, as in the failing heart. Cardiac output will also increase or decrease in parallel with stroke volume if there is no change in heart rate. The curves show how the heart performs at different states of contractility, ranging from the normal heart to one in cardiogenic shock. This is a condition where the cardiac output is insufficient to maintain tissue perfusion. Also shown is the curve for an increasing level of physical activity, which requires a corresponding increase in cardiac output.

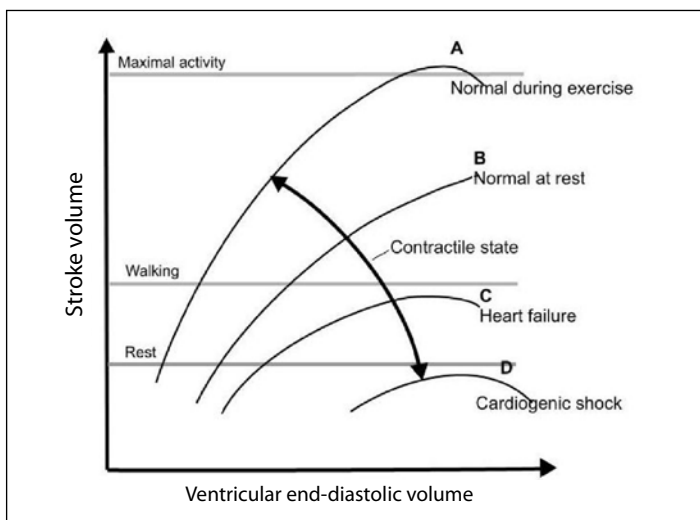


Figure 1. Starling's Law - Curves A and B illustrate the rise in cardiac output with increases in ventricular end-diastolic volume (pre-load) in the normal heart. Note that with an increase in contractility there is a greater cardiac output for the same ventricular end-diastolic volume. In the diseased heart (C and D) cardiac output is less and falls if ventricular end diastolic volume rises to high levels, as in heart failure or overload

Afterload is the resistance to ventricular ejection. Assuming the aortic valve is normal, this is caused by the resistance to flow in the systemic circulation and is the systemic vascular resistance (SVR). The resistance is determined by the diameter of the arterioles and pre-capillary sphincters; the narrower or more constricted, the higher the resistance. The level of SVR is controlled by the sympathetic system which controls the tone of the muscle in the wall of the arteriole, and hence the diameter. The resistance is measured in units of dyne.sec. cm^{-5} . A series of Starling curves with differing afterloads is shown in Figure 2, demonstrating a fall in stroke volume as afterload increases. The relationship between systemic vascular resistance and the control of arterial pressure is discussed below.

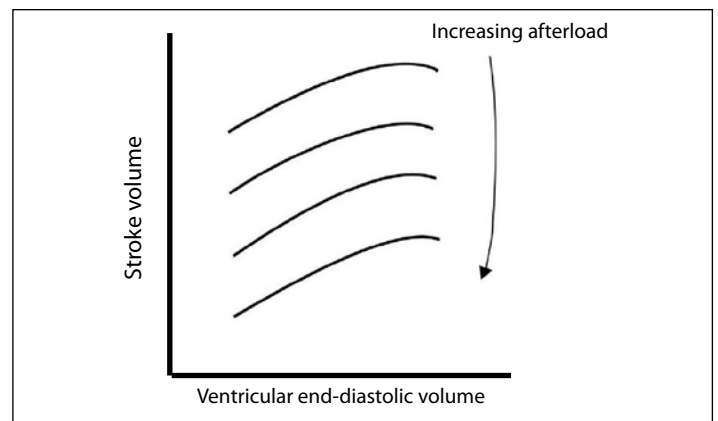


Figure 2. The relationship between stroke volume and afterload. A series of curves illustrate the effects of increasing afterload on systemic vascular resistance. As afterload increases, the patient moves to a lower curve, with a lower stroke volume for the same ventricular end-diastolic volume (preload)

Contractility describes the ability of the myocardium to contract in the absence of any changes in preload or afterload. In other words, it is the 'power' of the cardiac muscle. The most important influence on contractility is the sympathetic nervous system. Beta-adrenergic receptors are stimulated by norepinephrine (noradrenaline) released from nerve endings, and contractility increases. A similar effect is seen with circulating epinephrine (adrenaline) and drugs such as ephedrine, digoxin and calcium. Contractility is reduced by acidosis, myocardial ischaemia, and the use of beta-blocking and anti-arrhythmic agents.

Cardiac output will change to match changing metabolic demands of the body. The outputs of both ventricles must be identical, and also equal the venous return of blood from the body. The balancing of cardiac output and venous return is illustrated during the response to exercise. Blood vessels dilate in exercising muscle groups because of increased metabolism, and blood flow increases. This increases venous return and right ventricular preload. Consequently more blood is delivered to the left ventricle and cardiac output increases. There will also be increased contractility and heart rate from the sympathetic activity associated with exercise, further increasing cardiac output to meet tissue requirements.

CONTROL OF HEART RATE

The heart will beat independently of any nervous or hormonal influences. This spontaneous rhythm of the heart (called intrinsic automaticity) can be altered by nervous impulses or by circulatory substances, like epinephrine. The muscle fibres of the heart are excitable cells like other muscle or nerve cells, but have a unique property. Each cell in the heart will spontaneously contract at a regular rate because the electrical properties of the cell membrane spontaneously alter with time and regularly "depolarise". Depolarisation means that the electrical gradient across the cell membrane becomes less negative and then reverses, causing muscle contraction or passage of a nervous impulse. Muscle fibres from different parts of the heart have different rates of spontaneous depolarisation; the cells from the ventricle are the slowest, and those from the atria are faster.

The coordinated contraction of the heart is produced because the cells with the fastest rate of depolarisation "capture" the rest of the heart

muscle cells. These cells with the fastest rate of depolarisation are in the sinoatrial node (SA node), the “pacemaker” of the heart, found in the right atrium. As the SA node depolarises, a wave of electrical activity spreads out across the atria to produce atrial contraction. Electrical activity then passes through the atrioventricular node (AV node) and through into the ventricles via the Purkinje fibres in the Bundle of His to produce a ventricular contraction. If there is any disease of the conducting system of the heart, then this process may be interfered with and the heart rate altered. If, for example, there is disease of the AV node, then there is an electrical block between the atria and the ventricles. The ventricles will beat with their own inherent rhythm, which is much slower, usually 30-50 beats per minute.

Anaesthetic drugs, like halothane, may depress the rate of depolarisation of the SA node, and the AV node may become the pacemaker of the heart. When this occurs it is frequently termed nodal or junctional rhythm. This automatic rhythm of the heart can be altered by the autonomic nervous system. The sympathetic nervous system supply to the heart leaves the spinal cord at the first four thoracic vertebra, and supplies most of the muscle of the heart. Stimulation via the cardiac beta-1 receptors causes the heart rate to increase and beat more forcefully. The vagus nerve also supplies the atria, and stimulation causes the heart rate to decrease (bradycardia). Surgical procedures can cause vagal stimulation and produce severe bradycardia. Examples include pulling on the mesentery of the bowel, anal dilatation or pulling on the external muscles of the eye. Under normal conditions the vagus nerve is the more important influence on the heart. This is especially noticeable in athletes who have slow heart rates.

There are nervous reflexes that effect heart rate. The afferents (i.e. going to the brain) are nerves in the wall of the atria or aorta that respond to stretch. The aorta contains high pressure receptors. When the blood pressure is high these cause reflex slowing of the heart to reduce the cardiac output and the blood pressure. Similarly, when the blood pressure is low, the heart rate increases, as in shock. Similar pressure receptors are found in the atria. When the atria distend, as in heart failure or overtransfusion, there is a reflex increase in the heart rate to pump the extra blood returning to the heart. When there is a sudden reduction in the pressure in the atria the heart slows. This is called the Bainbridge Reflex and is the cause for the marked bradycardia sometimes seen during spinal anaesthesia. It is best treated by raising the legs to increase the venous return. Early administration of a cardioaccelerator such as ephedrine or epinephrine is recommended if there is no immediate response to this manoeuvre.

Circulatory substances can also affect the heart rate. Catecholamines, like epinephrine, are released during stress, and will cause an increase in heart rate. Drugs are another common cause of change in the heart rate and most anaesthetic drugs can do this. Halothane affects the SA node and will also depress the force of contraction of the heart. Isoflurane, by contrast has little direct affect on the heart, but causes peripheral vasodilation of the blood vessels. This will then decrease the blood pressure, and hence produce a reflex tachycardia as explained above. Administration of greater than 1 MAC of desflurane or isoflurane may increase sympathetic outflow and so increase heart

rate transiently and acutely; this does not happen with sevoflurane. Ketamine causes stimulation of the sympathetic nervous system, and therefore produces a tachycardia. Other circulating substances may also affect the heart rate, acting indirectly through the autonomic nervous system. For example, increased blood concentrations of carbon dioxide will cause stimulation of the sympathetic nervous system and tachycardia, and this is an important sign of respiratory failure.

THE SYSTEMIC CIRCULATION

The systemic blood vessels are divided into arteries, arterioles, capillaries and veins. Arteries supply blood to the organs at high pressure, whereas arterioles are smaller vessels with muscular walls, which allow direct control of flow through each capillary bed. Capillaries consist of a single layer of endothelial cells, and the thin walls allow exchange of nutrients between blood and tissue. Veins return blood from the capillary beds to the heart, and contain 70% of the circulating blood volume, in contrast to 15% in the arterial system. Veins act as a reservoir, and venous tone is important in maintaining the return of blood to the heart, for example in severe haemorrhage, when sympathetic stimulation causes venoconstriction.

BLOOD FLOW

The relationship between flow and driving pressure is given by the Hagen-Poiseuille formula. This states that flow rate in a tube is proportional to:

$$\frac{\text{driving pressure} \times \text{radius}^4}{\text{length} \times \text{viscosity}}$$

In blood vessels flow is pulsatile rather than continuous, and viscosity varies with flow rate, so the formula is not strictly applicable. However, it illustrates an important point; small changes in radius result in large changes in flow rate. In both arterioles and capillaries changes in flow rate are brought about by changes in tone and therefore vessel radius.

Viscosity describes the tendency of a fluid to resist flow. At low flow rates the red blood cells stick together, increasing viscosity, and remain in the centre of the vessel. The blood closest to the vessel wall (which supplies side branches) therefore has a lower haematocrit. This process is known as ‘plasma skimming’. Viscosity is reduced in the presence of anaemia, and the resulting increased flow rate helps maintain oxygen delivery to the tissues.

CONTROL OF THE SYSTEMIC CIRCULATION

Arteriolar tone determines blood flow to the capillary beds. A number of factors influence arteriolar tone, including autonomic control, circulating hormones, endothelium derived factors and the local concentration of metabolites.

Autonomic control is largely by the sympathetic nervous system, which supplies all vessels except the capillaries. Sympathetic fibres arise from the thoracic and lumbar segments of the spinal cord. These are under the control of the vasomotor centre in the medulla, which has distinct vasoconstrictor and vasodilator areas. Although there is a baseline sympathetic discharge to maintain vascular tone, increased stimulation affects some organs more than others (Figure 3). This tends to redistribute blood from skin, muscle and gut to brain, heart

and kidney. Increased sympathetic discharge is one of the responses to hypovolaemia, for example in severe blood loss, with the effect of protecting blood supply to the vital organs. The predominant sympathetic influence is vasoconstriction via alpha-adrenergic receptors. However, the sympathetic system also causes vasodilation via beta-adrenergic and cholinergic receptor stimulation, but only in skeletal muscle. This increased blood flow to muscle is an important part of the 'fight or flight' reaction, when exercise is anticipated.

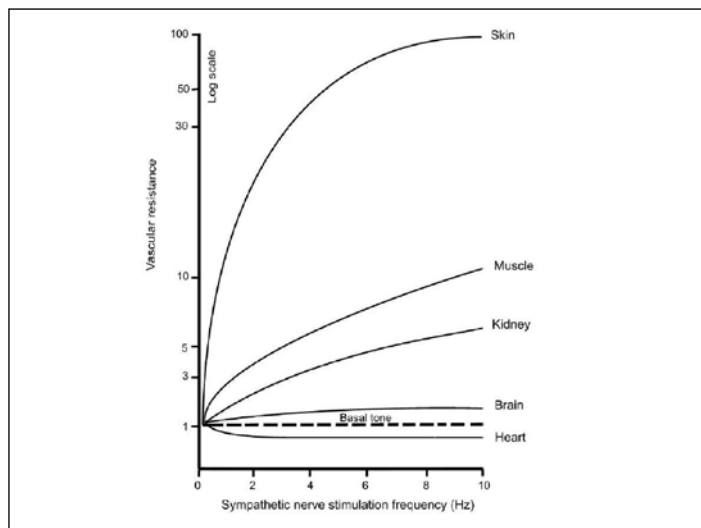


Figure 3. The effects of sympathetic nervous stimulation on vascular resistance in different organs. Note that for the same sympathetic stimulation, the resistance is higher in skin

Circulating hormones such as epinephrine and angiotensin II are potent vasoconstrictors, but they probably have little effect on acute cardiovascular control. In contrast, endothelium derived factors play an important role in controlling local blood flow. These substances are either produced or modified in the vascular endothelium, and include prostacyclin and nitric oxide, both potent vasodilators. An accumulation of metabolites such as CO_2 , K^+ , H^+ , adenosine and lactate causes vasodilation. This response is probably an important mechanism of autoregulation, the process whereby blood flow through an organ is controlled locally, and remains constant over a wide range of perfusion pressure. Autoregulation is a particular feature of the cerebral and renal circulations.

CONTROL OF ARTERIAL PRESSURE

Systemic arterial pressure is controlled closely in order to maintain tissue perfusion. The mean arterial pressure (MAP) takes account of pulsatile blood flow in the arteries, and is the best measure of perfusion pressure to an organ. MAP is defined as diastolic arterial pressure plus one third of the pulse pressure, where pulse pressure is the difference between systolic and diastolic arterial pressure. MAP is the product of cardiac output (CO) and systemic vascular resistance (SVR) and can be thought of as analogous to Ohm's law ($V=IR$):

$$\text{MAP} = \text{CO} \times \text{SVR}$$

If cardiac output falls, for example when venous return decreases in hypovolaemia, MAP will also fall unless there is a compensatory rise in SVR by vasoconstriction of the arterioles. This response is mediated by **baroreceptors**, which are specialised sensors of pressure

located in the carotid sinus and aortic arch, and connected to the vasomotor centre in the brainstem. A fall in blood pressure causes reduced stimulation of the baroreceptors, and consequent reduced discharge from the baroreceptors to the vasomotor centre. This causes an increase in sympathetic discharge leading to vasoconstriction, increased heart rate and contractility, and secretion of epinephrine. Conversely, rises in blood pressure stimulate the baroreceptors, which leads to increased parasympathetic outflow to the heart via branches of the vagus nerve, causing slowing of the heart. There is also reduced sympathetic stimulation to the peripheral vessels causing vasodilation. Baroreceptor responses provide immediate control of blood pressure; if hypotension is prolonged, other mechanisms start to operate, such as the release of angiotensin II and aldosterone from the kidneys and adrenal glands, which leads to salt and water being retained in the circulation.

The Valsalva manoeuvre is a simple test of the baroreceptor reflex. The patient tries to breathe out forcefully against a closed larynx resulting in an increased intrathoracic pressure. This causes decreased venous return, cardiac output and a fall in blood pressure leading to reduced baroreceptor discharge to the vasomotor centre. This then causes peripheral vasoconstriction, and an increase in heart rate, which is the normal response. This has the effect of maintaining systolic pressure, although the pulse pressure is reduced due to vasoconstriction.

CARDIOVASCULAR RESPONSES TO ANAESTHESIA

All anaesthetic agents have a direct depressant effect on the myocardium. Therefore they reduce myocardial contractility, and many also reduce sympathetic stimulation of the vascular system. The result is a decreased cardiac output accompanied by vasodilation, causing hypotension. This fall in blood pressure can compromise perfusion of vital organs, especially at induction of anaesthesia in the hypovolaemic patient. In contrast, agents such as ketamine and ether increase sympathetic activity, which opposes the direct depressant effect. Thus cardiac output and blood pressure are maintained despite the direct myocardial depressant action. Volatile anaesthetic agents reduce discharge from the sinoatrial node. This can lead to junctional rhythms, when the atrioventricular node takes over as pacemaker, associated with an absent P wave on the ECG. Local anaesthetic agents depress conduction of the cardiac impulse. This effect can be therapeutic, for example in the treatment of ventricular arrhythmias with lidocaine.

Controlled ventilation in a paralysed patient has many effects on the cardiovascular system. Firstly it increases intrathoracic pressure, which reduces venous return and preload, causing a fall in cardiac output. Secondly, changes in the partial pressure of carbon dioxide (PaCO_2) resulting from changes in ventilation will also have cardiovascular effects. A low PaCO_2 , which commonly occurs during controlled ventilation, causes peripheral vasoconstriction by a direct effect. This increases systemic vascular resistance, increases afterload and can result in a fall in cardiac output. It also causes cerebral vasoconstriction, reducing cerebral blood volume. A high PaCO_2 usually occurs in the anaesthetised patient during spontaneous breathing, and causes vasodilation and increased sympathetic activity, leading to increased cardiac output. However, the heart will be more likely to develop arrhythmias, particularly when using volatile agents.

Spinal and epidural anaesthesia blocks sympathetic nerves as well as sensory and motor fibres. This can lead to marked hypotension due to arteriolar and venous dilation because the sympathetic nerves to the lower extremities are blocked. Cardiac sympathetic nerve fibres,

which arise from the high thoracic spinal cord, may also be blocked, allowing an unopposed vagal action on the heart. In this case there will not be an appropriate increase in heart rate, and blood pressure will fall further.

Originally published in *Update in Anaesthesia*, edition 18 (2004) and reprinted from 'The College Bulletin' by kind permission of the Board of Management and Trustees of the British Journal of Anaesthesia

Aspects of Myocardial Physiology

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Summary

This article describes in more detail the physiology of the cardiac action potentials (nodal and Purkinje cell), the mechanics of the cardiac cycle and the control of coronary artery perfusion.

CARDIAC ACTION POTENTIALS

Action potentials (APs) are sequential changes in transmembrane potential that occur as a result of activity of ion channels, resulting in the propagation of electrical impulses in excitable cells. The heart has a multicellular structure but behaves like a syncytium because the individual muscle cells communicate with their neighbours through gap junctions, which provide low resistance pathways for easy movement of action potentials between cells. The cardiac action potential (~250ms) is much longer than those of nerve or skeletal muscle (~1-3ms). This is due to a prolonged plateau phase caused by calcium ion influx. Two types of action potential occur in the heart: The fast response, found in heart muscle and Purkinje fibres (Figure 1) and the slow response, found in pacemaker tissues such as the sinoatrial and atrioventricular nodes (Figure 2).

The fast response (Figure 1)

The resting potential of cardiac muscle and Purkinje fibres is about -90mV (interior negative to exterior). An AP is initiated when the membrane is depolarised to a threshold potential of about -65mV. The initial depolarisation originates from transmission from an adjacent cell via gap junctions.

Phase 0 - Rapid depolarization

The inward current caused by opening of fast Na⁺ channels becomes large enough to overcome the outward current through K⁺ channels resulting in a very rapid upstroke.

Phase 1 - Early incomplete repolarisation

Due to inactivation of fast Na⁺ channels and efflux of K⁺ ions.

Phase 2 - Plateau phase

A period of slow decay mainly due to Ca²⁺ entering the cell via L-type (L=long lasting) Ca²⁺ channels which are activated slowly when the membrane potential is more positive than about -35mV. This is balanced by K⁺ efflux through various K⁺ channels. Calcium entry during the plateau is essential for contraction; blockers of L-type Ca²⁺ channels (e.g. verapamil) reduce the force of contraction.

Phase 3 - Rapid repolarisation

Ca²⁺ influx declines and the K⁺ outward current becomes dominant, with an increased rate of repolarisation.

Phase 4 - Electrical diastole

Resting membrane potential is restored.

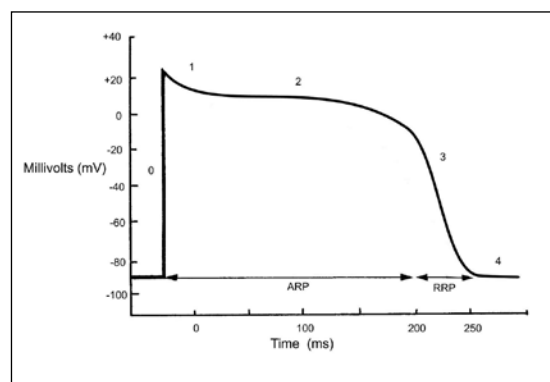


Figure 1. The fast response (Purkinje fibre) action potential; ARP – absolute refractory period, RRP – relative refractory period

The slow response (Figure 2)

These cells spontaneously depolarise and are said to have *automaticity*. Phases 1 and 2 are absent.

Phase 4 - Prepotential or pacemaker potential

There is no depolarisation plateau and the cells have an unstable resting membrane potential during this phase; they gradually depolarise from -60mV to a threshold of -40mV due to a slow continuous influx of Na⁺ ions and a decreased efflux of K⁺ ions. A Ca²⁺ current, due to the opening of T-type (T=transient) Ca²⁺ channels, completes the pacemaker potential.

Phase 0 - Depolarisation

When the membrane potential reaches threshold potential, the L-type calcium channels open, causing Ca²⁺ influx and an AP is generated.

Phase 3 - Repolarisation

Due to efflux of K⁺.

Norepinephrine and epinephrine (mediated via β_1 -receptors) increase the slope of phase 4 by increasing

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Ca^{2+} influx, therefore increasing the heart rate. Ca^{2+} influx also increases the force of contraction. Acetylcholine (mediated via M2 receptors) decreases the slope of phase 4 by increasing K^{+} efflux and causing hyperpolarisation (increased negativity within the cells). This makes the conduction tissue much less excitable so it takes longer to spontaneously reach the threshold level. This results in a decrease in heart rate. The intrinsic rate of the SA node is 100 per minute, however vagal tone decreases this to about 70 beats per minute.

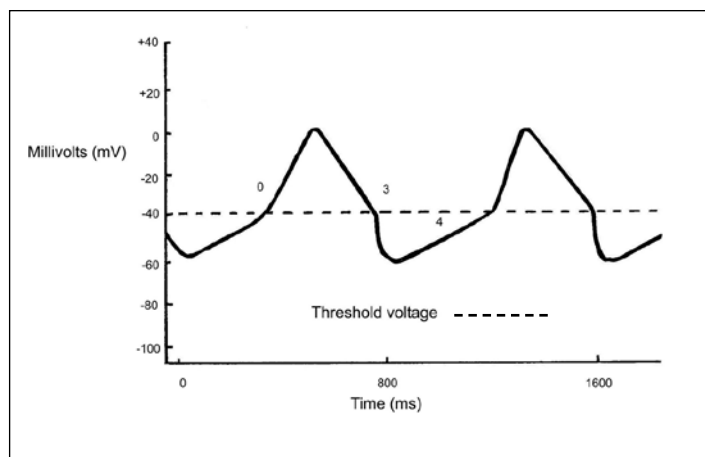


Figure 2. The slow response (sinoatrial node) action potential

Refractory periods

During the absolute refractory period (ARP) (Figure 1) the cardiac cell is totally inexcitable. During the following relative refractory period (RRP) there is a gradual recovery of excitability. A supramaximal stimulus can elicit an AP in the RRP. This AP, however, has a slower rate of depolarisation, a lower amplitude and shorter duration than normal and, therefore, the contraction produced is weaker. Peak muscle tension occurs just before the end of the ARP and the muscle is halfway through its relaxation phase by the end of the RRP. The long refractory period protects the ventricles from too rapid a re-excitation, which would impair their ability to relax long enough to refill sufficiently with blood. Unlike skeletal muscle, two contractions cannot summate and a fused titanic contraction cannot occur.

THE CARDIAC CYCLE

The cardiac cycle refers to the relationship between electrical, mechanical (pressure and volume) and valvular events occurring during one complete heartbeat (Figure 3).

Isovolumetric ventricular contraction (early systole)

The action potential is conducted through the AV node, down the bundle of His, across both ventricles and ventricular depolarisation occurs. This is the QRS complex of the ECG. Ventricular contraction causes a sharp rise in ventricular pressure, and the AV valves close (first heart sound) once this exceeds atrial pressure, preventing backflow into the atria. Ventricular pressure increases dramatically with no change in ventricular volume. During this initial phase of ventricular contraction pressure is less than in the pulmonary artery and aorta, so the outflow valves remain closed - the ventricular volume does not change.

The increasing pressure causes the AV valves to bulge into the atria, resulting in the 'c' wave of the central venous pressure trace.

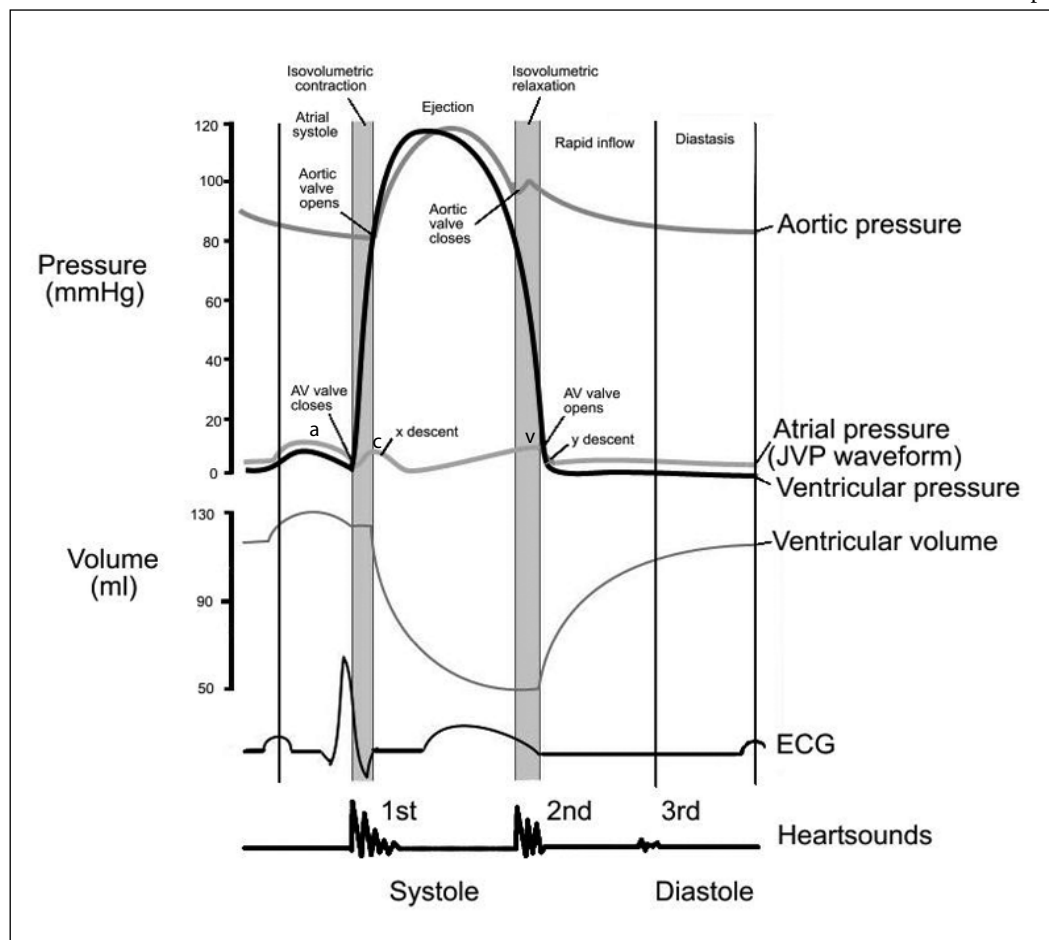


Figure 3. Events of the cardiac cycle

Ejection (systole)

The semilunar valves open as ventricular pressure exceeds aortic blood pressure. Approximately two thirds of the blood in the ventricles is ejected into the arteries. Flow into the arteries is initially very rapid (**rapid ejection phase**), but subsequently decreases (**reduced ejection phase**). The stroke volume (SV) is the volume of blood ejected from each ventricle in a single beat and the ejection fraction is SV/EDV (end diastolic volume). Arterial blood pressure rises to its highest point (systolic blood pressure). During the last two thirds of systole, before the AV valves open again, atrial pressure rises as a result of filling from the veins, resulting in the 'v' wave of the central venous

pressure trace. Active contraction ceases during the second half of ejection, and the ventricular muscle repolarises. This is the T wave of the ECG. Ventricular pressure during the reduced ejection phase is slightly less than in the artery, but blood continues to flow out of the ventricle because of momentum (**protodiastole**). Eventually, the flow briefly reverses, causing closure of the outflow valve and a small increase in aortic pressure, the **dicrotic notch**.

Isovolumetric relaxation (early diastole)

The ventricles relax and the ventricular pressure falls below arterial blood pressure. This causes the semilunar valves to close causing the second heart sound. The ventricular pressure falls with no change in ventricular volume. When ventricular pressure falls below atrial pressure, the AV valves open and the cycle begins again.

Passive filling (early diastole)

The atria and ventricles are relaxed and ventricular pressure is close to zero. The atrioventricular (AV) valves are open and the semilunar valves are closed. Blood flows from the great veins into the atria and ventricles. About 80% of ventricular filling occurs during this phase consisting of an initial **rapid filling** phase followed by a slower filling phase (**diastasis**).

Atrial contraction (late diastole)

A wave of depolarisation, beginning at the sinoatrial (SA) node, spreads across both atria and reaches the AV node. This is the P wave of the ECG. The atria contract and atrial pressures increases producing the 'a' wave of the central venous pressure trace. Blood continues to flow into the ventricles and ventricular pressure increases slightly. The atrial contribution to ventricular filling increases as heart rate increases and diastole shortens, and there is less time for passive filling. Ventricular

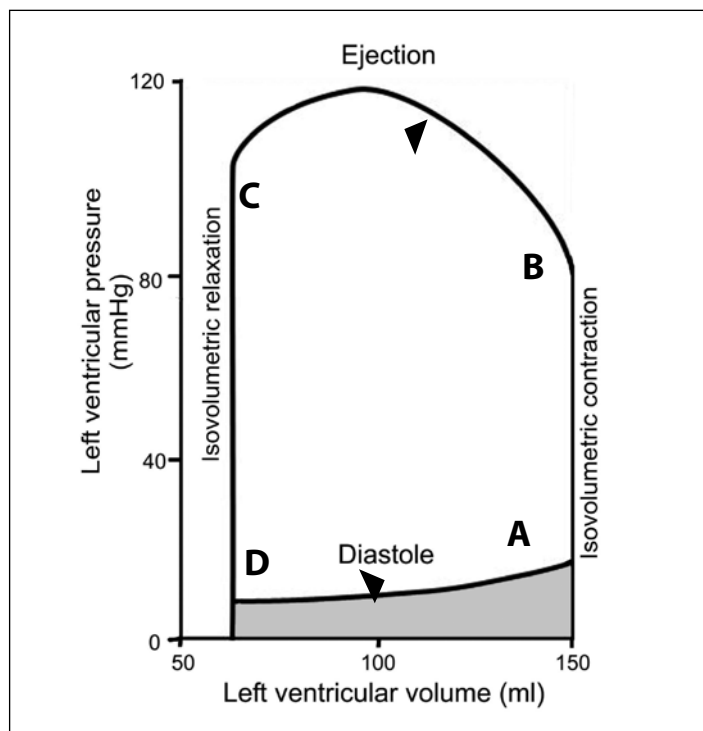


Figure 4. Left ventricular pressure-volume loop during a single heart cycle in a normal adult at rest

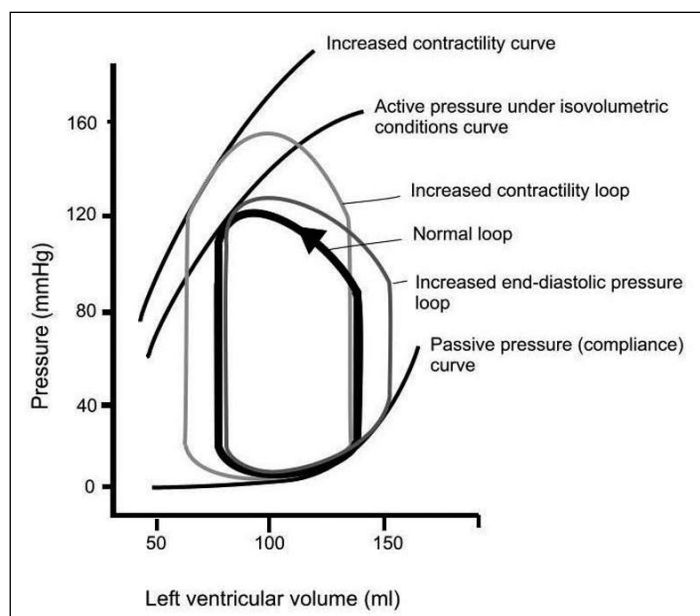


Figure 5. How the pressure-volume loop is affected by the contractility and compliance of the ventricle, and factors that alter refilling or ejection

volume (EDV) = volume of blood in the ventricle at the end of diastole. Arterial pressure is at its lowest at this stage of the cycle.

The X descent of the CVP trace results from atrial relaxation and downward displacement of the tricuspid valve during ventricular systole. The Y descent of the CVP trace is due to atrial emptying as the tricuspid valve opens and blood enters the ventricle.

THE PRESSURE VOLUME LOOP (Figures 4 and 5)

This represents the events of the cardiac cycle. The cardiac cycle proceeds in an anticlockwise direction. (A) End diastole, (B) aortic valve opening, (C) aortic valve closure, (D) mitral valve opening. EDV and end systolic volume (ESV) are represented by points A and C respectively. The area enclosed by the loop represents the stroke work (since work = pressure x volume). The pressure-volume curve in diastole is initially quite flat, indicating that large increases in volume can be accommodated by only small increases in pressure. However, the ventricle becomes less distensible with greater filling, as evidenced by the sharp rise of the diastole curve at large intraventricular volumes.

CONTROL OF THE CORONARY CIRCULATION

Myocardial blood supply is from the right and left coronary arteries, which run over the surface of the heart giving branches to the endocardium (the inner layer of the myocardium). Venous drainage is mostly via the coronary sinus into the right atrium, but a small proportion of blood flows directly into the ventricles through the Thebesian veins, delivering unoxygenated blood to the systemic circulation.

The heart at rest receives about 5% of the cardiac output. Coronary blood flow is approximately 250ml.min⁻¹. Oxygen extraction by the myocardium at rest is very high (65%) compared to other tissues (35%). Therefore, the myocardium cannot compensate for reductions in blood flow by extracting more oxygen from haemoglobin. Any increases in myocardial O₂ demand must be met by an increase in

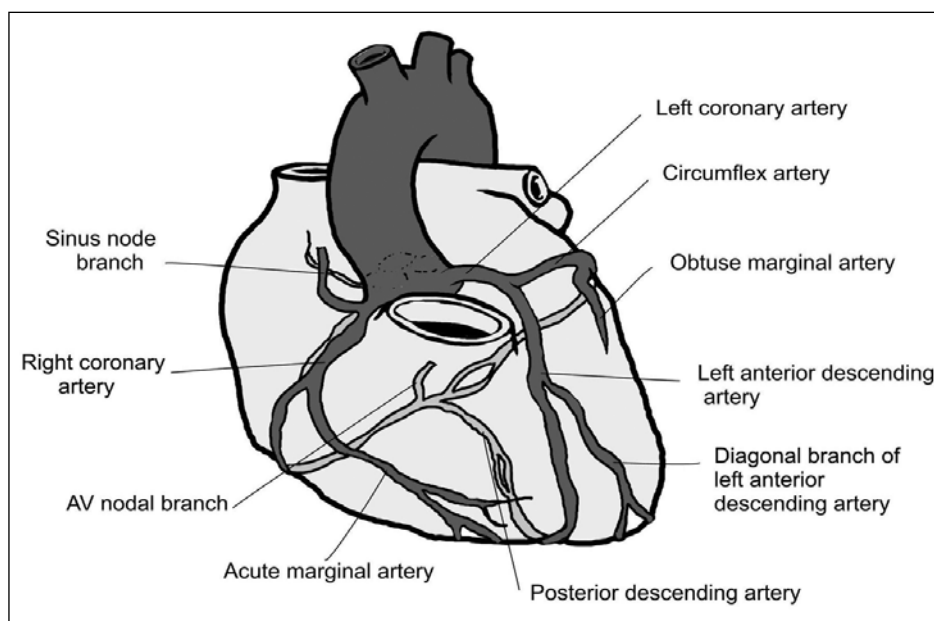


Figure 6. *The anatomy of the coronary arteries*

coronary blood flow. The three main factors influencing coronary flow are **mechanical**, mainly external compression and perfusion pressure, **metabolic** and **neural**.

Coronary artery compression and blood flow

Left coronary arterial blood flow is unique in that there is interruption of flow during systole (mechanical compression of vessels by myocardial contraction) and flow occurs predominantly during diastole when cardiac muscle relaxes and no longer obstructs blood flow through ventricular vessels. Conversely, right coronary arterial flow rate is highest during systole, because the aortic pressure driving flow increases more during systole (from 80 to 120mmHg) than the right ventricular pressure, which opposes flow (from 0 to 25mmHg). As about 80% of the total coronary arterial flow occurs during diastole, a pressure around the aortic diastolic pressure becomes the primary determinant of the pressure gradient for coronary flow. Coronary perfusion pressure is the arterial diastolic pressure minus left ventricular end diastolic pressure ($CPP = ADP - LVEDP$). Increases in heart rate that shorten diastole time for coronary blood flow are likely to increase oxygen consumption more than elevations in blood pressure, which are likely to offset increased oxygen demands by enhanced pressure-dependent coronary blood flow. The myocardium

regulates its own blood flow (autoregulation) closely between perfusion pressures of 50 and 150mmHg. Beyond this range, blood flow becomes increasingly pressure dependent. This autoregulation is due to a combination of myogenic and metabolic mechanisms.

Metabolic factors

The close relationship between coronary blood flow and myocardial oxygen consumption indicates that one or more of the products of metabolism cause coronary vasodilation. Hypoxia and adenosine are potent coronary vasodilators. Others factors suspected of playing this role include $PaCO_2$, H^+ , K^+ , lactate and prostaglandins. Under normal conditions, changes in blood flow are entirely due to variations in coronary artery tone (resistance) in response to metabolic demand.

Neural Factors

The coronary arterioles contain α_1 -adrenergic receptors which mediate vasoconstriction, and β_2 -adrenergic receptors which mediate vasodilation. Sympathetic stimulation generally increases myocardial blood flow because of metabolic factors, and not because of β_2 -adrenergic stimulation. This is shown experimentally when the inotropic and chronotropic effects of sympathetic discharge are blocked by a β_1 selective blocker to reduce metabolic demand, and injection of norepinephrine in unanesthetized animals elicits coronary vasoconstriction. Therefore the direct effect of sympathetic stimulation is constriction rather than dilation of the coronary vessels and highlights the importance of metabolic control.

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Respiratory Physiology

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Summary

This article covers the main areas of respiratory physiology that are important to anaesthetists. Examples relevant to anaesthesia and pathological states of the respiratory system are used when possible. Further detail is included in the following articles on oxygen delivery and carbon dioxide transport. Some areas are covered in more than one article, but are included since alternative explanations from different authors may enhance understanding of more difficult aspects of this subject.

INTRODUCTION

The main function of the lungs is to provide continuous gas exchange between inspired air and the blood in the pulmonary circulation, supplying oxygen and removing carbon dioxide, which is then cleared from the lungs by subsequent expiration. Survival is dependent upon this process being reliable, sustained and efficient, even when challenged by disease or an unfavourable environment. Evolutionary development has produced many complex mechanisms to achieve this, several of which are compromised by anaesthesia. A good understanding of respiratory physiology is essential to ensure patient safety during anaesthesia.

MECHANISM OF BREATHING

A pressure gradient is required to generate airflow. In spontaneous respiration, inspiratory flow is achieved by creating a sub-atmospheric pressure in the alveoli (of the order of $-5\text{cmH}_2\text{O}$ during quiet breathing) by increasing the volume of the thoracic cavity under the action of the inspiratory muscles. During expiration the intra-alveolar pressure becomes slightly higher than atmospheric pressure and gas flow to the mouth results.

Motor pathways

The main muscle generating the negative intrathoracic pressure that produces inspiration is the diaphragm, a musculotendinous sheet separating the thorax from the abdomen. Its muscular part is peripheral, attached to the ribs and lumbar vertebrae, with a central tendon. Innervation is from the phrenic nerves (C3-5) with contraction moving the diaphragm downwards forcing the abdominal contents down and out. Additional inspiratory efforts are produced by the external intercostal muscles (innervated by their intercostal nerves T1-12) and the accessory muscles of respiration (sternomastoids and scalenes), although the latter only become important during exercise or respiratory distress.

During quiet breathing expiration is a passive process, relying on the elastic recoil of the lung and chest wall. When ventilation is increased (such as during exercise) expiration becomes active, with contraction of the muscles of the abdominal wall and the internal intercostals.

Central control

The mechanism by which respiration is controlled is complex. There is a group of respiratory centres located in the brainstem producing automatic breathing activity. This is then regulated mainly by input from chemoreceptors. This control can be overridden by voluntary control from the cortex. Breath-holding, panting or sighing at will are examples of this voluntary control.

The main respiratory centre is in the floor of the 4th ventricle, with inspiratory (dorsal) and expiratory (ventral) neurone groups. The inspiratory neurones fire automatically, but the expiratory ones are used only during forced expiration. The two other main centres are the apneustic centre, which enhances inspiration, and the pneumotaxic centre, which terminates inspiration by inhibition of the dorsal neurone group above.

The **chemoreceptors** that regulate respiration are located both centrally and peripherally. Normally, control is exercised by the central receptors located in the medulla, which respond to the CSF hydrogen ion concentration, in turn determined by CO_2 , which diffuses freely across the blood-brain barrier from the arterial blood. The response is both quick and sensitive to small changes in arterial pCO_2 (PaCO_2). In addition, there are peripheral chemoreceptors located in the carotid and aortic bodies most of which respond to a fall in O_2 , but some also to a rise in arterial CO_2 . The degree of hypoxia required to produce significant activation of the O_2 receptors is such that they are not influential under normal circumstances, but will do so if profound hypoxia ($\text{PaO}_2 < 8\text{kPa}$) occurs, for example at high altitude when breathing air (see later in Special circumstances). It also happens when the response to CO_2 is impaired, which can occur if the PaCO_2 is chronically elevated, leading to a blunting of the central receptor sensitivity.

RESPIRATORY PROCESS

Respiratory values

The various terms used to describe lung excursion (movement) during quiet and maximal respiration are shown in Figure 1 below.

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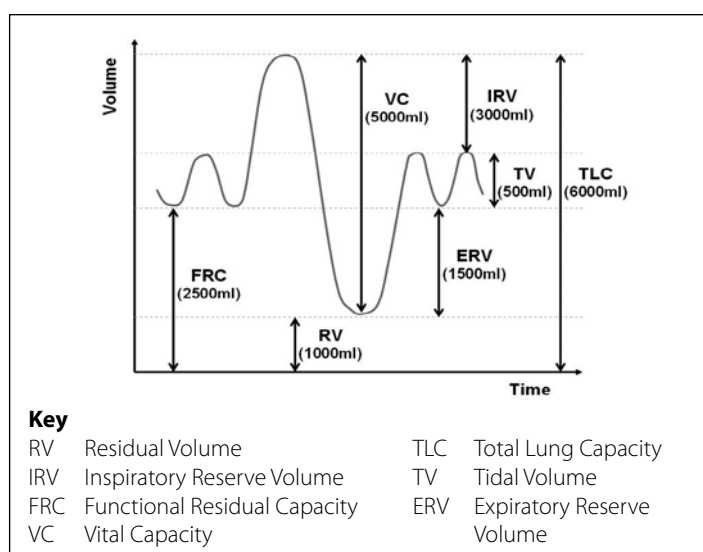


Figure 1. Lung volumes in an adult male measured with a spirometer during quiet breathing with one maximum breath

The tidal volume (500ml) multiplied by the respiratory rate (14 breaths.min⁻¹) is the minute volume (7000ml.min⁻¹): TV x RR = MV. Not all of the tidal volume takes part in respiratory exchange, as this process does not start until the air or gas reaches the respiratory bronchioles (division 17 of the respiratory tree). Above this level the airways are solely for conducting, their volume being known as the anatomical deadspace. The volume of the anatomical deadspace is approximately 2ml.kg⁻¹ or 150ml in an adult, roughly a third of the tidal volume. The part of the tidal volume which does take part in respiratory exchange multiplied by the respiratory rate is known as the alveolar ventilation (approximately 5000ml.min⁻¹).

Functional residual capacity (FRC) is the volume of air in the lungs at the end of a normal expiration. The point at which this occurs (and hence the FRC value) is determined by a balance between the inward elastic forces of the lung and the outward forces of the respiratory cage (mostly due to muscle tone). FRC falls with lying supine, obesity, pregnancy and anaesthesia, though not with age. The FRC is of particular importance to anaesthetists because:

- During apnoea it is the reservoir to supply oxygen to the blood.
- As it falls the distribution of ventilation within the lungs changes leading to mismatching with pulmonary blood flow.
- If it falls below a certain volume (the closing capacity), airway closure occurs leading to shunt.

Resistance and compliance

In the absence of respiratory effort, the lung will come to lie at the point of the FRC. To move from this position and generate respiratory movement, two aspects need to be considered, which oppose lung expansion and airflow, and therefore need to be overcome by respiratory muscle activity. These are the airway resistance and the compliance of the lung and chest wall.

Resistance of the airways describes the obstruction to airflow provided by the conducting airways, resulting largely from the larger airways (down to division 6-7), plus a contribution from tissue resistance

produced by friction as tissues of the lung slide over each other during respiration. An increase in resistance resulting from airway narrowing, such as bronchospasm, leads to obstructive airways disease. In obstructive airways disease, it might be expected that airflow could be improved by greater respiratory effort (increasing the pressure gradient) to overcome the increase in airways resistance. Whilst this is normally true for inspiration, it is not necessarily the case during expiration, as the increase in intrapleural pressure may act to compress airways proximal to the alveoli, leading to further obstruction with no increase in expiratory flow and air-trapping distally. This is shown in Figure 2 and demonstrates why expiration is usually the major problem during an asthmatic attack.

Compliance denotes distensibility (stretchiness) and in a clinical setting refers to the lung and chest wall combined, being defined as the volume change per unit pressure change (V/P). When compliance is low, the lungs are stiffer and more effort is required to inflate the alveoli. Conditions that worsen compliance, such as pulmonary fibrosis, produce restrictive lung disease. Compliance also varies within the lung according to the degree of inflation, as shown in Figure 2. Poor compliance is seen at low volumes (because of difficulty with initial lung inflation) and at high volumes (because of the limit of chest wall expansion), with best compliance in the mid-expansion range.

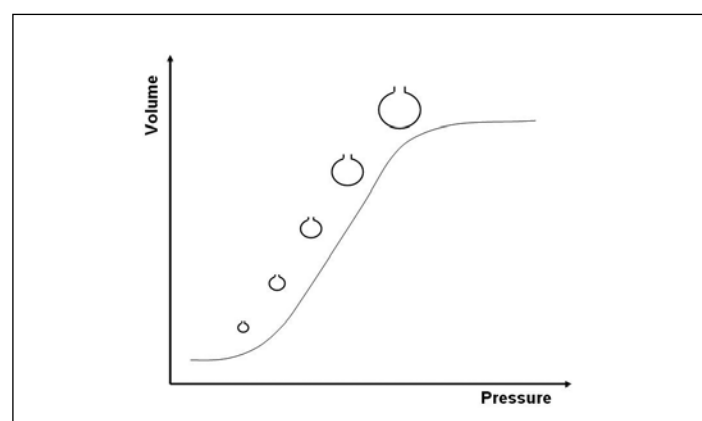


Figure 2. Compliance curve showing compliance within the lung at different levels of inflation. At FRC in the young healthy individual the apices are well-inflated (towards the top of the curve) and therefore less ventilated than the midzones and bases, which are on the lower, steeper part of the compliance curve

Work of breathing

Of the two barriers to respiration, airway resistance and lung compliance, it is only the first of these which requires actual work to be done to overcome it. Airway resistance to flow is present during both inspiration and expiration and the energy required to overcome it, which represents the work of breathing, is dissipated as heat.

Although energy is required to overcome compliance in expanding the lung, it does not contribute to the actual work of breathing as it is not dissipated, but converted to potential energy in the distended elastic tissues. Some of this stored energy is used to do the work of breathing produced by airways resistance during expiration. The work of breathing is best displayed on a pressure-volume curve of one respiratory cycle (Figure 3), which shows the different pathways

for inspiration and expiration, known as **hysteresis**. The total work of breathing of the cycle is the area contained in the loop.

With high respiratory rates, faster airflow rates are required, increasing the frictional forces. This is more marked in obstructive airways disease and such patients therefore generally minimise the work of breathing by using a slow respiratory rate and large tidal volumes. In contrast, patients with restrictive lung disease (poor compliance) reach the unfavourable upper part of the compliance curve soon, as the tidal volume increases. The pattern of breathing seen in such patients usually involves small tidal volumes and a fast respiratory rate.

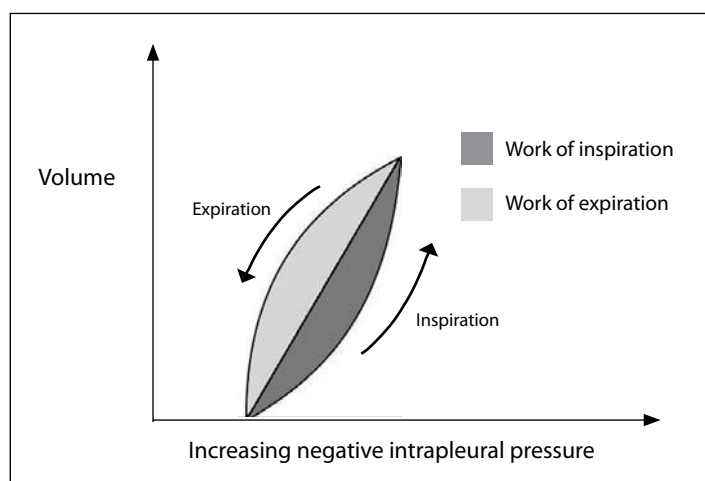


Figure 3. Work of breathing shown on a lung pressure-volume (compliance) curve

Surfactant

Any liquid surface exhibits surface tension, a tendency for the molecules on the surface to pull together. This is why, when water lies on a surface, it forms rounded droplets. If the surface tension is reduced, for example by adding a small amount of soap, the droplets collapse and the water becomes a thin film.

When a liquid surface is spherical, it acts to generate a pressure within the sphere according to Laplace's law:

$$\text{Pressure} = \frac{2 \times \text{surface tension}}{\text{radius of sphere}}$$

The film of liquid lining the alveoli exhibits surface tension in such a manner to increase the pressure in the alveoli, with a greater rise in small alveoli than in large ones. Surfactant is a substance secreted by type II alveolar epithelial cells, which lowers the surface tension of this respiratory surface liquid markedly. Mainly consisting of a phospholipid (dipalmitoyl lecithin), its physiological benefits are:

- A reduction in the fluid leak from pulmonary capillaries into the alveoli, as the surface tension forces act to increase the hydrostatic pressure gradient from capillary to alveolus.
- An increase (improvement) in overall lung compliance.
- A reduction in the tendency for small alveoli to empty into large ones, reducing the tendency for the lung to collapse.

Diffusion of oxygen

The alveoli provide an enormous surface area for gas exchange with pulmonary blood (between 50-100m²), with a thin membrane across which gases must diffuse. The solubility of oxygen is such that its diffusion across the normal alveolar-capillary membrane is an efficient and rapid process. Under resting conditions pulmonary capillary blood is in contact with the alveolus for about 0.75 seconds in total and is fully equilibrated with alveolar oxygen after only about a third of the way along this course. If lung disease is present which impairs diffusion, there is therefore still usually sufficient time for full equilibration of oxygen when at rest. During exercise, however, the pulmonary blood flow is quicker, shortening the time available for gas exchange, and so those with lung disease are unable to oxygenate the pulmonary blood fully and thus have a limited ability to exercise.

For carbon dioxide, which diffuses across the alveolar-capillary membrane 20 times faster than oxygen, the above factors are less liable to compromise transfer from blood to alveoli.

Ventilation, perfusion and shunt

In an ideal situation the ventilation delivered to an area of lung would be just sufficient to provide full exchange of oxygen and carbon dioxide with the blood perfusing that area. In the normal setting, whilst neither ventilation (V) nor perfusion (Q) is distributed evenly throughout the lung, their matching is fairly good, with the bases receiving substantially more of both than the apices (Figure 4).

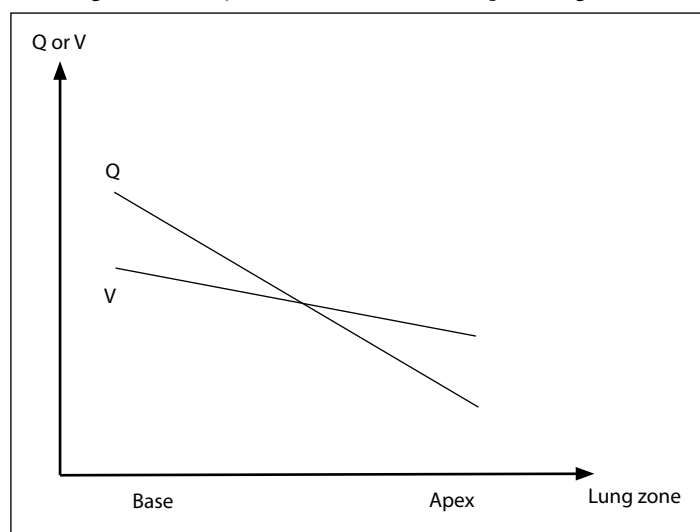


Figure 4. Distribution of ventilation (V) and perfusion (Q) in the lung

For **perfusion**, the distribution throughout the lung is largely due to the effects of gravity. Therefore in the upright position this means that the perfusion pressure at the base of the lung is equal to the mean pulmonary artery pressure (15mmHg or 20cmH₂O) plus the hydrostatic pressure between the main pulmonary artery and lung base (approximately 15cmH₂O). At the apices the hydrostatic pressure difference is subtracted from the pulmonary artery pressure with the result that the perfusion pressure is very low, and may at times even fall below the pressure in the alveoli leading to vessel compression and intermittent cessation of blood flow.

The distribution of **ventilation** across the lung is related to the position of each area on the compliance curve at the start of a normal

tidal inspiration (the point of the FRC). Because the bases are on a more favorable part of the compliance curve than the apices, they gain more volume change from the pressure change applied and thus receive a greater degree of ventilation. Although the inequality between bases and apices is less marked for ventilation than for perfusion, overall there is still good **V/Q matching** and efficient oxygenation of blood passing through the lungs.

This traditional explanation of the relationship between ventilation and perfusion has recently been challenged. There is increasing evidence that physiological matching of ventilation and perfusion, despite considerable apparent heterogeneity in both, is achieved by a common pattern of asymmetric branching of the airways and blood vessels.¹

Disturbance of this distribution can lead to V/Q mismatching (Figure 5). For an area of low V/Q ratio the blood flowing through it will be incompletely oxygenated, leading to a reduction in the oxygen level in arterial blood (hypoxaemia). Providing some ventilation is occurring in an area of low V/Q, the hypoxaemia can normally be corrected by increasing the FiO_2 , which restores the alveolar oxygen delivery to a level sufficient to oxygenate the blood fully.

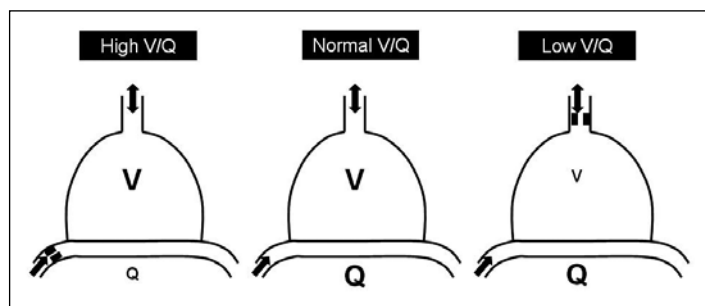


Figure 5. Ventilation/perfusion (V/Q) mismatch

V/Q mismatch occurs very commonly during anaesthesia because the FRC falls, leading to a change in the position of the lung on the compliance curve. The apices, therefore, move to the most favorable part of the curve whilst the bases are located on a less favorable part at the bottom of the curve.

At the extremes of V/Q mismatch, an area of lung receiving no perfusion will have a V/Q ratio of ∞ (infinity) and is referred to as **alveolar deadspace**, which together with the anatomical deadspace makes up the physiological deadspace. Ventilating the deadspace is in effect wasted ventilation, but is unavoidable.

In contrast, in an area of lung receiving no ventilation, owing to airway closure or blockage, the V/Q ratio will be zero and the area is designated as **shunt**. Blood will emerge from an area of shunt with a pO_2 unchanged from the venous level (5.3kPa) and produce marked arterial hypoxaemia. This hypoxaemia cannot be corrected by increasing the FiO_2 , even to 1.0, as the area of shunt receives no ventilation at all. The well-ventilated parts of the lung cannot compensate for the area of shunt because haemoglobin is fully saturated at a normal pO_2 . Increasing the pO_2 of this blood will not increase the oxygen content substantially.

In the case of shunt, therefore, adequate oxygenation can only be re-established by restoring ventilation to these areas using measures

such as physiotherapy, PEEP or CPAP, which clear blocked airways and re-inflate areas of collapsed lung. Because closing capacity (CC) increases progressively with age, and is also higher in neonates, these patients are at particular risk during anaesthesia as the FRC may fall below CC causing airway closure.

A physiological mechanism exists which reduces the hypoxaemia resulting from areas of low V/Q ratio, by producing local vasoconstriction in these areas and diverting blood to other, better-ventilated parts of the lung. This effect, known as hypoxic pulmonary vasoconstriction (HPV), is mediated by unknown local factors. The protective action of HPV is, however, inhibited by various drugs, including inhalational anaesthetic agents.

CONTROL OF RESPIRATION

Anaesthesia affects respiratory function in different ways. Knowledge of respiratory physiology is necessary to understand these effects. Physiological control systems involving the nervous system usually have three components. These are:

- A central controlling area
- An afferent pathway
- An efferent pathway.

The neurones (nerve cells) of the controlling area integrate the information from other parts of the body and produce a coordinated response. This response from the central controlling area is carried to the various organs and muscles along efferent pathways. The input to the central controlling area is from the various sensors via the afferent pathways.

Central controlling area

The central controlling area for breathing, called the **respiratory centre**, is in the lower part of the brain stem, in the medulla oblongata. There are “inspiratory neurones” which are active during inspiration and inactive during expiration. Other neurones are active during expiration but not inspiration - the “expiratory neurones”. These two groups of neurones automatically maintain a rhythmic cycling pattern of inspiration and expiration. This automatic rhythm can be modified by afferent information.

Afferent supply

Central chemoreceptors

Chemoreceptors are cells that respond to chemical stimuli. There are cells in the floor of the fourth ventricle (part of the brainstem) that respond to the acidity of the cerebrospinal fluid (CSF) and the output from these cells influences breathing. The acidity of any fluid is measured by the pH; this is related to the number of hydrogen ions in the solution.

The normal pH of the body is 7.4, a higher pH than this represents alkaline conditions in the body with a lower hydrogen ion concentration. A pH less than 7.4 represent acidic conditions, with a higher hydrogen ion concentration. The cells in the floor of the fourth ventricle respond to the pH of the CSF. An acidic CSF causes hyperventilation - this is the reason for dyspnoea with conditions such as diabetic ketoacidosis. An alkaline CSF inhibits the respiratory

centre. Carbon dioxide in the blood can rapidly diffuse across into the CSF and there is a balance between the level of carbon dioxide, hydrogen ions and bicarbonate ions in the CSF.

If the carbon dioxide in the blood increases (e.g. following exercise), then the carbon dioxide, hydrogen ion and bicarbonate ion concentrations increase correspondingly in the CSF. This increase in CSF acidity causes hyperventilation which lowers the carbon dioxide concentration in the blood. A low blood carbon dioxide level (hypocarbica) has the opposite effect and may occur, for example, following controlled ventilation during anaesthesia. This may delay the return of spontaneous breathing at the end of surgery.

Peripheral chemoreceptors

The carotid and aortic bodies are small pieces of tissue that contain chemoreceptors which respond to the oxygen and carbon dioxide concentrations in arterial blood. The carotid body is the more important of the two and is situated at the division of the common carotid artery into the external and internal carotid arteries in the neck. The aortic body is found on the aortic arch. The information from the carotid body is carried along the glossopharyngeal nerve (the ninth cranial nerve) and the information from the aortic body is along the vagus nerve (the tenth cranial nerve), to the respiratory centre. The output from the carotid body is thought to provide information to allow immediate regulation of breathing, breath by breath, by the respiratory centre.

In normal people, if the arterial blood reaching the carotid body has a partial pressure of oxygen of 10kPa (80mmHg) or a carbon dioxide partial pressure of more than approximately 5kPa, (40mmHg), then there is an immediate and marked increase in breathing. These limits can be modified by disease or age; for example, people with chronic bronchitis may tolerate an increased concentration of carbon dioxide or a decreased concentration of oxygen in the blood.

Brain

Breathing can be influenced by other parts of the brain. We can all consciously breathe deeply and more rapidly (called hyperventilation), and this can happen, for example, before starting strenuous exercise. Intensely emotional situations, for example, distressing sights, will also cause hyperventilation. Hyperventilation is also part of the response to massive blood loss. This response is co-ordinated by the autonomic system in the hypothalamus and the vasomotor centre in the brain stem.

Lung

There are various receptors in the lung that modify breathing. Receptors in the wall of the bronchi respond to irritant substances and cause coughing, breath holding and sneezing. In the elastic tissues of the lung and the chest wall are receptors that respond to stretch. The exact function of these receptors is not fully understood, but is thought to be responsible for various reflexes that have been discovered in laboratory studies of animals. There are stretch responses that occur when the lung and chest wall are distended and inhibit further inspiration. This is an obvious safety mechanism to avoid overdistension. Conversely, when the lung volume is low,

then there are opposite reflexes. A small increase in lung size may stimulate stretch receptors to cause further inspiration. This can sometimes be seen in anaesthetised patients who have been given an opioid; spontaneous breathing may be absent or very slow, but if the patient is given a small positive pressure breath by the anaesthetist, then inspiration is stimulated and the patient takes a deep breath. This reflex may also have some function in newborn babies just after delivery, when small breaths may stimulate further inspiration.

There are also stretch receptors in the blood vessels in the lung. If these are stretched, as in heart failure, the response is to hyperventilate. The information from these receptors in the lung is carried to the respiratory centre along the vagus nerve.

Efferent supply

The efferent nerves from the respiratory centre pass down the spinal cord to the diaphragm, intercostal muscles and accessory muscles of inspiration in the neck. The diaphragm is supplied by the phrenic nerve, that is formed in the neck from the spinal nerves, C3, 4 and 5. The intercostal muscles are supplied by the segmental intercostal nerves that leave the spinal cord between T1 and T12. The accessory muscles in the neck are supplied from the cervical plexus. During normal breathing, inspiration is an active muscular process. Expiration is passive and relies on the natural elasticity of the tissues to deflate the lung. The most important muscle for inspiration is the diaphragm. Any disease that affects the efferent pathways from the respiratory centre to C3, 4 and 5 and then the phrenic nerve to the diaphragm, may cause severe difficulty in breathing. Trauma to the cervical cord, above C3, is normally fatal for this reason.

Anaesthetic drugs and respiration

Opioid drugs, such as morphine or fentanyl, depress the respiratory centre's response to hypercarbia. These effects can be reversed by naloxone. Volatile anaesthetic agents depress the respiratory centre in a similar fashion, although ether has less effect on respiration than the other agents. Volatile agents also alter the pattern of blood flow in the lungs, resulting in increased ventilation/perfusion mismatch and decreasing the efficiency of oxygenation. Nitrous oxide has only minor effects on respiration. The depressant effects of opioids and volatile agents are additive and close monitoring of respiration is necessary when they are combined. When oxygen is not available respiration should always be supported during anaesthesia.

NON-RESPIRATORY LUNG FUNCTIONS

Whilst the main function of the lung is for respiratory gas exchange, it has several other important physiological roles including; a reservoir of blood available for circulatory compensation, a filter for circulating microaggregates, activation of angiotensin II from angiotensin I by angiotensin converting enzyme (ACE), inactivation of several substances such as norepinephrine and bradykinin, and an immunological function by secreting IgA into bronchial mucus.

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The Physiology of Oxygen Delivery

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OXYGEN TRANSPORT FROM THE AIR TO THE TISSUES

Oxygen is transported from the air that we breathe to each cell in the body. In general, gases move from an area of high concentration (or pressure) to areas of low concentration (or pressure). If there is a mixture of gases in a container, the pressure of each gas (the partial pressure, indicated by the symbol P) is equal to the pressure that each gas would produce if it occupied the container alone. The total pressure of the gas mixture is the sum of the partial pressures of all the individual gases.

Oxygen cascade

Oxygen moves down the pressure or concentration gradient from a relatively high level in air, to the levels in the respiratory tract and then alveolar gas, the arterial blood, capillaries and finally the cell (see Figure 1). The PO_2 reaches the lowest level (1-1.5kPa) in the mitochondria, the structures in cells responsible for

energy production. This decrease in PO_2 from air to the mitochondrion is known as the oxygen cascade. The successive steps down in PO_2 occur for physiological reasons, but they can be influenced by pathological states, for instance hypoventilation, ventilation/perfusion inequality, or diffusion abnormality, that will result in tissue hypoxia.

Atmosphere to alveolus

The air (atmosphere) around us has a total pressure of 101kPa (1 atmosphere of pressure = 760mmHg = 101kPa). Air is made up of 21% oxygen, 78% nitrogen and small quantities of CO_2 , argon and helium. The pressure exerted by oxygen and nitrogen, when added together, approximates to atmospheric pressure. The pressure of oxygen (PO_2) of dry air at sea level is therefore 21.2kPa ($21/100 \times 101 = 21.2$ kPa). However by the time the inspired air reaches the trachea it has been warmed and humidified by the upper respiratory tract. The humidity is formed by water vapour which

Summary

In order to survive, humans have to be able to extract oxygen from the atmosphere and transport it to their cells where it is utilised for essential metabolic processes. Some cells can produce energy without oxygen (anaerobic metabolism) for a short time, although it is inefficient. Other organs, for example the brain, are made up of cells that can only produce the energy necessary for survival in the presence of a continual supply of oxygen (aerobic metabolism). Tissues differ in their ability to withstand anoxia (lack of oxygen) - the brain and the heart are the most sensitive.

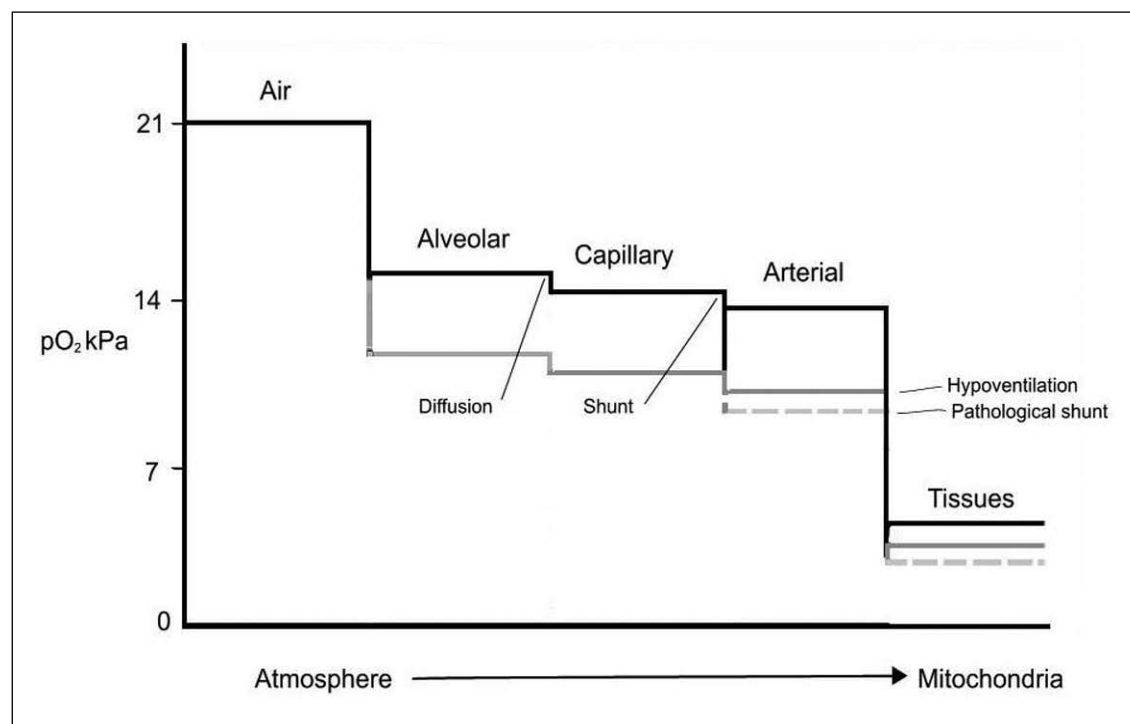


Figure 1. The oxygen cascade. The effects of hypoventilation are shown as the grey line and the effects of a pathological shunt are shown as a dashed line

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is a gas, so exerts a pressure. At 37°C the water vapour pressure in the trachea is 6.3kPa. Taking the water vapour pressure into account, the PO₂ in the trachea when breathing air is (101-6.3) × 21/100 = 19.9kPa. By the time the oxygen has reached the alveoli the PO₂ has fallen to about 13.4kPa. This is because the PO₂ of the gas in the alveoli (PAO₂) is further reduced by dilution with carbon dioxide entering the alveoli from the pulmonary capillaries. The PAO₂ can be calculated using the **alveolar gas equation**:

$$PAO_2 = FiO_2 - \frac{PaCO_2}{RQ}$$

Where RQ = the respiratory quotient, the ratio of CO₂ production to O₂ consumption, usually about 0.8

Alveolus to blood

Blood returning to the heart from the tissues has a low PO₂ (4.3kPa) and travels to the lungs via the pulmonary arteries. The pulmonary arteries form pulmonary capillaries, which surround alveoli. Oxygen diffuses (moves through the membrane separating the air and the blood) from the high partial pressure in the alveoli (13kPa) to the area of lower partial pressure - the blood in the pulmonary capillaries (4.3kPa). After oxygenation, blood moves into the pulmonary veins and returns to the left side of the heart, to be pumped to the systemic tissues. In a 'perfect lung', the PO₂ of pulmonary venous blood would be equal to the PO₂ in the alveolus (the PAO₂). Two main factors cause the PO₂ of pulmonary venous blood to be less than the PAO₂, that is, to increase the **alveolar:arterial difference**. These are ventilation/perfusion mismatch (either increased deadspace or shunt) and slow diffusion across the alveolar-capillary membrane.

Ventilation/perfusion (V/Q) mismatch

In a 'perfect lung' all alveoli would receive an equal share of alveolar ventilation and the pulmonary capillaries that surround different

alveoli would receive an equal share of cardiac output – i.e. alveolar minute ventilation and perfusion would be perfectly matched, V/Q = 1. Even in health this is not achieved and at almost all levels in a normal lung there is a relative imbalance of perfusion and ventilation (Figure 2). Perfusion is best at the base of the lung and gradually reduces towards the top of the lung, largely due to the effects of gravity. The alveoli at the base of a normal lung are at a lower resting volume in expiration (at functional residual capacity, FRC), but they are better ventilated (they increase their volume proportionately more) during inspiration. This concept is not intuitive and occurs because our major muscle of inspiration, the diaphragm, lies below

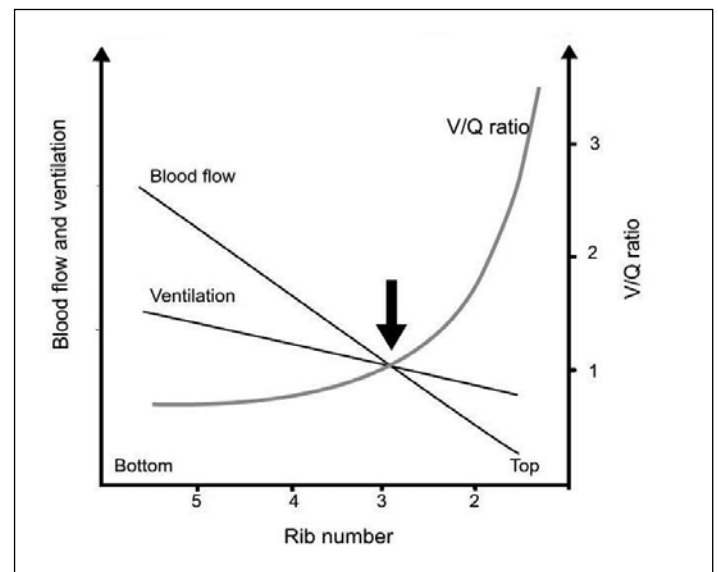


Figure 2. Graph to show perfusion and ventilation in different segments moving up the lung. Arrow indicates area of lung with perfect matching of ventilation to perfusion

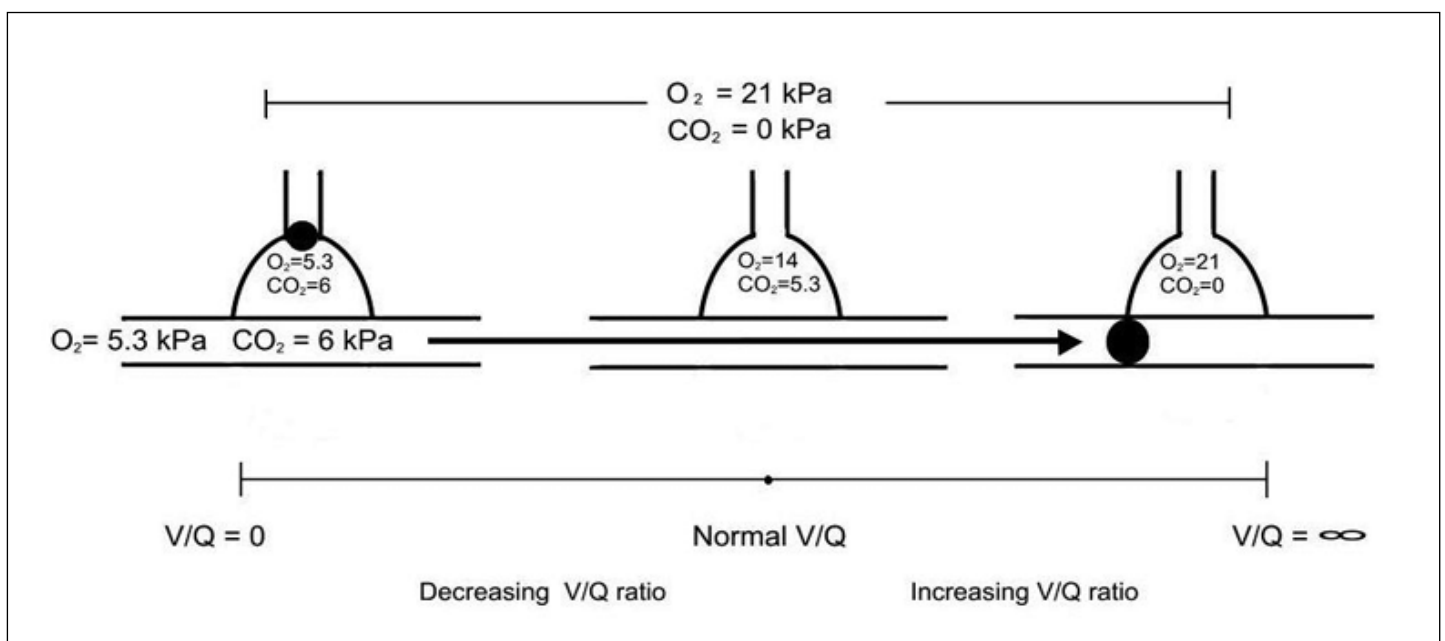


Figure 3. Schematic diagram showing 3 lung units. The ideal situation and the two extremes of V/Q mismatch, i.e. shunt and dead space, are shown

the lung contributing to better lung compliance towards the base of the lung. Both ventilation and perfusion improve as you move down the lung towards its base, but they are not perfectly matched. Areas at the top of the lung are relatively more ventilated than perfused (the extreme example of this is deadspace, where the lung volume is ventilated but there is insufficient perfusion for gas exchange to occur, $V/Q \gg 1$). Areas towards the base are perfused more than ventilated (the extreme example of this is a shunt, $V/Q \ll 1$). Both extreme examples of the spectrum of possible V/Q mismatches are illustrated in Figure 3.

Where blood flows past alveoli with no gas exchange taking place (shunt, see Figure 3), well ventilated alveoli (with high PO_2 in capillary blood) cannot compensate for the lack of oxygen transfer in the under-perfused alveoli with a low PO_2 in the capillary blood. This is because there is a maximum amount of oxygen that can combine with haemoglobin (this is shown by the oxygen-haemoglobin dissociation curve, later). Arterial oxygen, PAO_2 is therefore lower than the alveolar oxygen, PAO_2 .

Lung pathology that exacerbates the physiological shunt includes atelectasis, consolidation of the lung, pulmonary oedema or small airway closure. Pulmonary embolism causes increased physiological deadspace.

Diffusion

Oxygen diffuses from the alveolus to the capillary until the P_{cO_2} is equal to that in the alveolus. This process is rapid (about 0.25seconds) and is normally complete by the time the blood has passed about one third of the way along the pulmonary capillary. The total transit time through the capillary is 0.75seconds (see Figure 4a).

In the normal lung, even if the cardiac output and blood flow past the alveoli is increased during exercise, there is enough time for equilibration (Figure 4b). Pulmonary disease may cause an abnormality of the alveolar-capillary membrane, thus impairing transfer of oxygen from the alveolus to the capillary (diffusion abnormality). At rest there may still be time for the PAO_2 to equilibrate with alveolar oxygen, but on exercise full oxygen transfer is impossible and hypoxaemia develops (Figure 4c). However, the ability of the lung to compensate is great and problems caused by poor gas diffusion are a rare cause for hypoxia, except with diseases such as alveolar fibrosis.

Hypoxic pulmonary vasoconstriction

In order to minimize the detrimental effect that shunt has on oxygenation, the blood vessels in the lung are adapted to vasoconstrict in response to low oxygen levels and therefore reduce blood flow to areas that are underventilated. This is termed hypoxic pulmonary vasoconstriction and reduces the effect of shunt.

Oxygen carriage by the blood

Oxygen is carried in the blood in two forms. Most is carried combined with haemoglobin (Figure 5), and a small amount is dissolved in the plasma. Each gram of haemoglobin can carry 1.34ml of oxygen when fully saturated. Therefore every litre of blood with a Hb concentration of $15g.dl^{-1}$ can carry about 200ml of oxygen when fully saturated with oxygen (i.e. exposed to a PO_2 greater than 13kPa). At this PO_2 only 3ml of oxygen will dissolve in each litre of plasma.

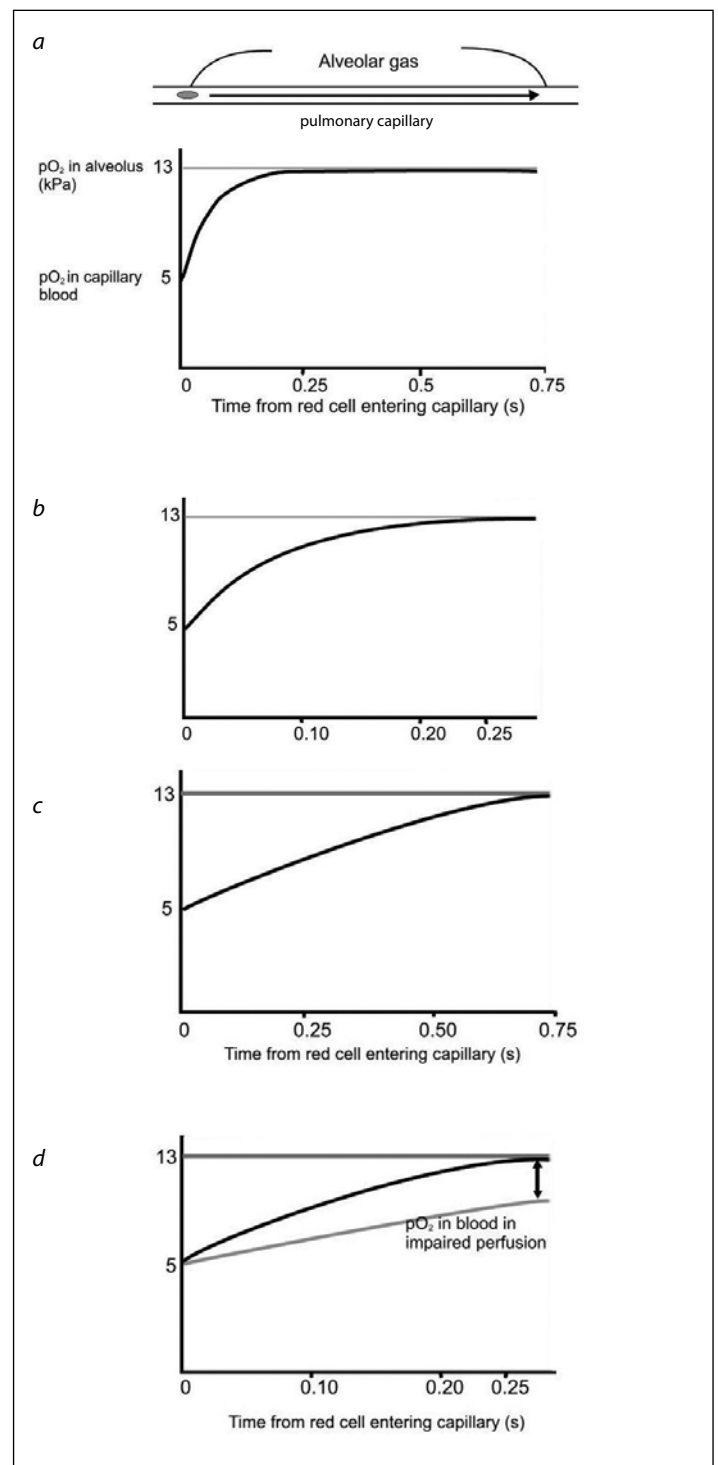


Figure 4. (a) Normal diffusion from alveolus to capillary during passage of blood along the capillary. By 0.25s the red cell haemoglobin is completely saturated and the partial pressure of oxygen in the blood equilibrates with that in the alveolus and therefore diffusion stops. (b) Diffusion of oxygen with increased cardiac output (note the shorter time scale on the x-axis). The red cell may only be in contact with alveolar gas for 0.25s, however this will still allow sufficient time to achieve full saturation. (c) Impaired oxygen diffusion where there is an abnormal alveolar-capillary membrane. Saturation is just achieved at rest (solid line), but there is insufficient time for full saturation when the cardiac output is increased (d). This results in exertional desaturation (arrow)

If the PAO_2 is increased significantly (by breathing 100% oxygen) then a small amount of extra oxygen will dissolve in the plasma (at a rate of $0.025\text{ml O}_2/100\text{ml of blood/kPa PO}_2$) but there will normally be no significant increase in the amount carried by haemoglobin, as it is already >95% saturated with oxygen.

Oxygen delivery

When considering the adequacy of oxygen delivery to the tissues, three factors need to be taken into account: haemoglobin concentration, cardiac output and oxygenation.

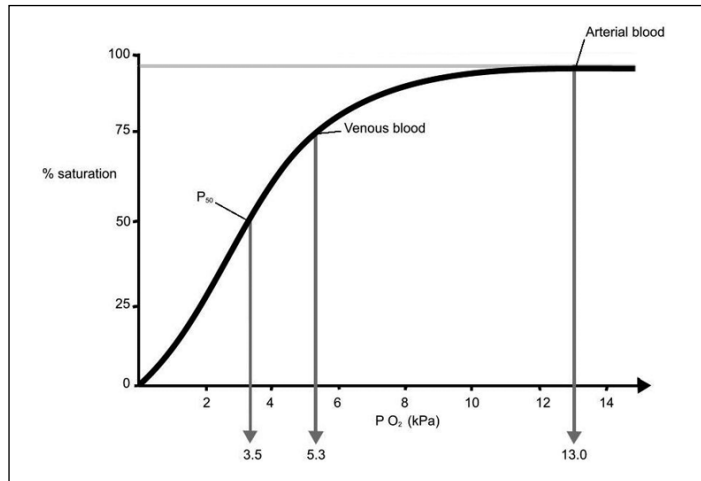


Figure 5. The oxygen-haemoglobin dissociation curve. The sigmoid curve arises because of 'positive cooperativity' of the 4 haemoglobin subunit – when the first subunit binds to oxygen a conformation (shape) change makes it more likely that the second and third subunits will bind to oxygen

The quantity of oxygen made available to the body in one minute is known as the oxygen delivery:

$$\begin{aligned} \text{Oxygen delivery (ml O}_2\cdot\text{min}^{-1}) &= \text{Cardiac output (l}\cdot\text{min}^{-1}) \times \text{Hb concentration (g}\cdot\text{l}^{-1}) \times 1.34 \text{ (ml O}_2\cdot\text{gHb}^{-1}) \times \% \text{ saturation} \\ &= 5000\text{ml}\cdot\text{min}^{-1} \times 200\text{ml O}_2\cdot 1000\text{ml blood}^{-1} \\ &= 1000\text{ml O}_2\cdot\text{min}^{-1} \end{aligned}$$

Oxygen consumption

Approximately 250ml of oxygen are used every minute by a conscious resting person (resting oxygen consumption) and therefore about 25% of the arterial oxygen content is used every minute. The haemoglobin in mixed venous blood is about 73% saturated (98% minus 25%).

At rest, oxygen delivery to the cells of the body exceeds oxygen consumption. During exercise, oxygen consumption increases. The increased oxygen requirement is usually provided by an increased cardiac output (as shown in the formula above). A low cardiac output, low haemoglobin concentration (anaemia) or low oxygen saturation will result in reduced tissue oxygen delivery, unless there is a compensatory change in one of the other factors.

If oxygen delivery falls relative to oxygen consumption, the tissues extract more oxygen from the haemoglobin and the saturation of mixed venous blood falls below 70%. Below a certain point, decreased oxygen delivery cannot be compensated for by an increased oxygen extraction, and this results in anaerobic metabolism and lactic acidosis. This situation is known as supply-dependent oxygenation.

OXYGEN STORES

In spite of our reliance on oxygen, the stores of oxygen in the body are small and would be unable to sustain life for more than a few minutes. If breathing ceases, oxygen stores are limited to the oxygen in the lung and oxygen in the blood. The amount of oxygen in the blood depends on the blood volume and haemoglobin concentration, as described above. The amount of oxygen in the lung is dependent on the lung volume at functional residual capacity (FRC) and the alveolar concentration of oxygen. The FRC is the volume of air (about 3 litres in an adult) that is present in the lungs at the end of a normal expiration; at this volume the elastic recoil of the lung (its tendency to collapse) is balanced by the tendency of the chest wall and diaphragm to resist lung collapse. When breathing air, the total oxygen stores (in blood and lung) are small. The major component of this store is the oxygen bound to haemoglobin (see Table 1); only a small part of these stores can be released without an unacceptable reduction in PAO_2 (when haemoglobin is 50% saturated, the PAO_2 will have fallen to 3.5kPa). Breathing 100% oxygen causes a large increase in the total oxygen stores as the FRC fills with oxygen. The major component of the store is now in the lung and 80% of this oxygen can be used without any reduction in haemoglobin saturation (PAO_2 is still about 14kPa). This is the reason why pre-oxygenation is so effective.

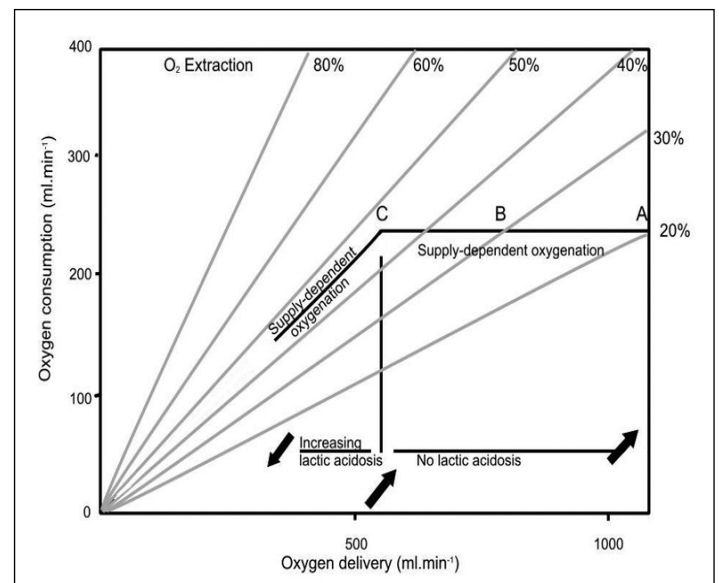


Figure 6. Graph showing the balance between oxygen delivery and oxygen consumption. The horizontal solid line shows the extent to which oxygen delivery can be reduced and compensated by an increase in oxygen extraction (normally between 20-30%, between A and B). Point C shows the point beyond which compensation is insufficient and oxygen consumption is limited by delivery (supply-dependent), and anaerobic metabolism, producing lactic acid, results

Table 1. Principal stores of oxygen in the body

	Breathing AIR	Breathing 100% O ₂
O ₂ store in the lungs at FRC	450ml	3000ml
O ₂ store bound to haemoglobin	850ml	950ml
O ₂ dissolved or bound in tissues	250ml	300ml
Total	1550ml	4250ml

OXYGEN TRANSPORT - THE EFFECTS OF ANAESTHESIA

Hypoventilation may occur during anaesthesia due to airway obstruction, the effects of volatile anaesthetic agents, opioids and other sedatives. Ketamine and ether (at less than 1 MAC) cause less respiratory depression than other anaesthetic agents. The PAO_2 is a balance between the oxygen supplied by breathing and that used by metabolic processes in the body. Hypoventilation and a decreased inspired oxygen concentration will therefore cause a reduction in PAO_2 . The increased utilisation of oxygen when metabolic rate is raised (e.g. during postoperative shivering or pyrexia) also causes a reduction in PAO_2 .

If the PAO_2 falls to less than 8kPa the aortic and carotid body chemoreceptors respond by causing hyperventilation and increasing cardiac output through sympathetic nervous system stimulation. This normal protective response to hypoxia is reduced by anaesthetic drugs. This effect extends into the postoperative period.

Following induction of anaesthesia there is a rapid reduction in FRC, largely attributable to loss of tone in the respiratory muscles and chest wall. FRC drops below the closing volume in the lung – the expiratory volume at which airway closure first occurs. This primarily occurs in small airways in dependant parts of the lung; these areas may remain closed throughout the respiratory cycle to result in a shunt.

As described above, V/Q mismatch due to airway closure (shunt) will increase the alveolar-arterial difference. This 'venous admixture' increases from 1% to around 10% following induction of anaesthesia. With the possible exception of patients spontaneously

breathing while anaesthetised with ketamine, this increase in venous admixture occurs irrespective of the anaesthetic agent used and whether muscle relaxants are used or not. It should be viewed as an unavoidable adverse effect of anaesthesia and explains the universal requirement for supplementary oxygen during surgery to achieve normal oxygenation. Furthermore, volatile anaesthetic agents suppress hypoxic pulmonary vasoconstriction, and blood flow to under-ventilated or collapsed alveoli is not reduced appropriately. In addition, many anaesthetic agents depress cardiac output and therefore decrease oxygen delivery.

Reduced tissue oxygen delivery during anaesthesia is partially compensated for by the fact that anaesthesia causes a 15% reduction in metabolic rate and therefore a reduction in oxygen requirements. Artificial ventilation causes a further 6% reduction in oxygen requirements as the work of breathing is removed. Anaesthetic agents do not affect the carriage of oxygen by haemoglobin.

PRACTICAL USE OF OXYGEN

Inspired oxygen concentration

The efficiency of oxygenation during anaesthesia is reduced due to hypoventilation and venous admixture. Inspired oxygen in the range of 25% to 30% is usually effective in restoring the PAO_2 to normal when hypoxaemia is due to hypoventilation (Figure 7).

When hypoxaemia is due to venous admixture it is possible to restore the PAO_2 by increasing the inspired oxygen concentration if the venous admixture does not exceed the equivalent of a 30% shunt (Figure 8).

The inspired oxygen concentration during maintenance of anaesthesia should routinely be increased to 30% whenever possible to compensate for hypoventilation and shunt which normally accompany anaesthesia. Additional oxygen may need to be administered to patients at risk of decreased oxygen delivery (anaemia or decreased cardiac output) or increased oxygen consumption (fever).

Pre-oxygenation

The small volume of the oxygen stores of a patient breathing air means that there will be a rapid fall in oxygen saturation during apnoea (e.g. following induction of anaesthesia, during laryngospasm or during upper airway obstruction). Pre-oxygenation involves breathing 100% oxygen for three minutes through an anaesthetic circuit with a face mask firmly applied to the face. This is the time taken to replace the nitrogen in the FRC with oxygen using normal tidal ventilation ('denitrogenation'). Although FRC falls on induction of anaesthesia the extra oxygen contained within the FRC provides an essential store of oxygen for periods of apnoea, particularly during rapid sequence induction or difficult intubation. Patients with a small FRC

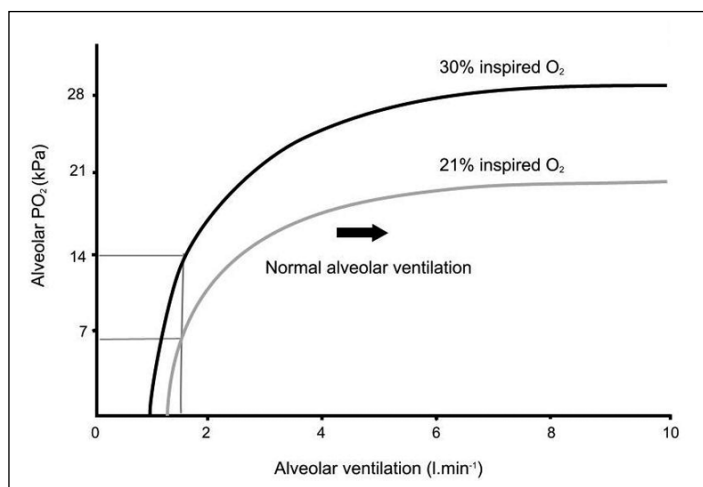


Figure 7. The effect on PAO_2 of increasing the FiO_2 from 21% (thin curve) to 30% (heavy curve) at a constant oxygen consumption of $200ml.min^{-1}$. The effect on PAO_2 of increasing the FiO_2 in a patient with an alveolar ventilation of $1.5l.min^{-1}$ is shown

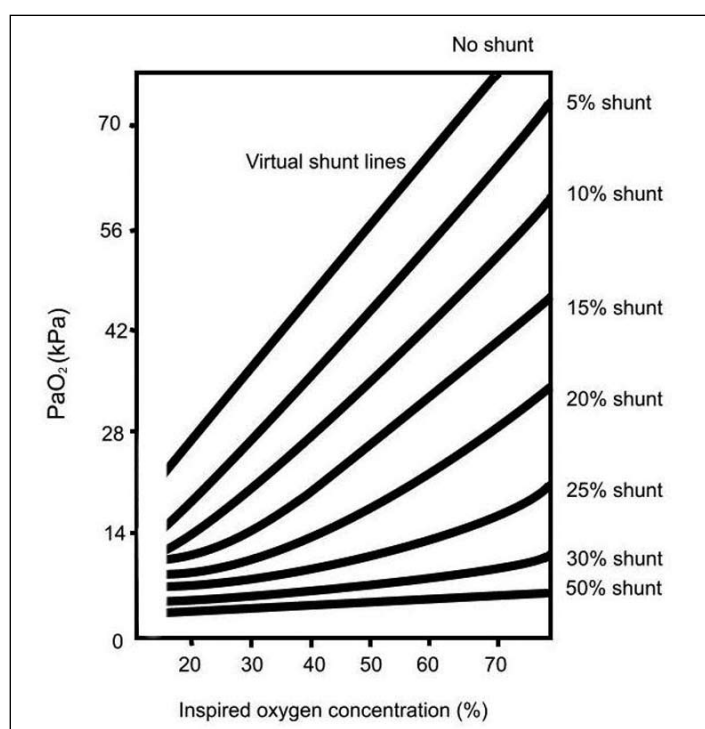


Figure 8. The effect on PaO_2 (vertical axis) of an increasing FiO_2 (horizontal axis) in the presence of different sized shunts. It can be seen that increasing the FiO_2 when the shunt is very large (greater than 50% of cardiac output) is ineffective in increasing PaO_2 .

(infants, pregnancy, the obese) or a low haemoglobin concentration, and therefore smaller oxygen stores, desaturate more rapidly and pre-oxygenation is especially indicated in these patients.

Crisis management

When managing emergencies during anaesthesia, consideration should always be given to the immediate administration of 100% oxygen, while the cause is found and rectified. It is the most appropriate treatment for acute deterioration in cardiorespiratory function.

Anoxic gas mixtures

If, during the course of an anaesthetic, 100% nitrous oxide is given to the patient in error, the fall in PaO_2 will be much more rapid than during apnoea. The PaO_2 can fall to dangerously low levels in as little as 10 seconds. This is because the oxygen in the patient's lungs and blood (oxygen stores) is being actively washed out with each breath that contains no oxygen. The fall in PaO_2 is therefore more rapid than would occur if it was only being used up by the metabolic needs of the body ($250\text{ml}\cdot\text{min}^{-1}$). Modern anaesthesia machines include a hypoxic link to prevent 100% nitrous oxide being administered in error.

Diffusion hypoxia

Nitrous oxide is forty times more soluble in blood than nitrogen. When nitrous oxide is discontinued at the end of anaesthesia, nitrous oxide diffuses out of the blood into the alveoli in large volumes during the next 2 to 3 minutes. If the patient is allowed to breathe air at this time the combination of nitrous oxide and nitrogen in the alveoli reduces the PaO_2 . This is called diffusion hypoxia and is

avoided by increasing the alveolar concentration of oxygen by the administration of 100% oxygen for 2 to 3 minutes after discontinuing nitrous oxide.

Postoperative oxygen

The causes of increased venous admixture (V/Q mismatch - shunt and airway closure) and the abnormal response to hypoxia continue into the postoperative period for up to three days following major surgery. Postoperative hypoventilation is common and may be due to the residual effect of anaesthesia, the use of opioid analgesia, pain or airway obstruction. Shivering in the immediate postoperative period causes an increase in oxygen consumption. Additional oxygen should therefore be given to all unconscious patients in recovery and to those awake patients who either shiver, hypoventilate, are desaturated or who are considered to be at increased risk (e.g. ischaemic heart disease).

On the ward during the postoperative period, episodes of airway obstruction during sleep are common and may aggravate borderline oxygenation due to the above factors. This is usually due to the use of opioid analgesia and a change in sleep pattern that occurs on the second and third postoperative nights. After major surgery, the risk of hypoxaemia extends well into the postoperative period. Small degrees of cyanosis are not easy to detect clinically, especially in anaemic patients, and therefore oxygen should be given to these patients wherever possible, especially overnight. Postoperative pain should be effectively treated, particularly following abdominal or thoracic surgery. If opioid analgesics are indicated, hypoventilation should be anticipated, and oxygen saturation monitored as a routine.

PROBLEMS ASSOCIATED WITH OXYGEN ADMINISTRATION

It has been suggested that high concentrations of oxygen (90-100%) administered to patients for a prolonged period (several days) may cause pulmonary damage. Whilst this is a concern, it should never prevent the use of oxygen to treat severe hypoxia. High concentrations of oxygen encourage collapse of alveoli with low ventilation/perfusion ratios. Oxygen is rapidly and completely absorbed from these alveoli and, when it is the only gas being given, these underventilated alveoli collapse (absorption atelectasis). When air and oxygen is used, the nitrogen present is absorbed more slowly and prevents the alveolus from collapsing. It is therefore sensible to administer the lowest FiO_2 that achieves adequate oxygenation (as guided by pulse oximetry).

Oxygen therapy may rarely depress ventilation in patients suffering from severe chronic obstructive airways disease. Patients who chronically retain CO_2 lose the hypercapnoeic stimulus to maintain ventilation and are therefore reliant on their hypoxic drive to self ventilate. Administration of oxygen may remove this drive and result in respiratory arrest. In practice this situation is rare, but again it is sensible to gradually titrate the FiO_2 to achieve a realistic oxygenation goal. It is often appropriate to tolerate moderate hypoxia in these patients (maximum SpO_2 90-94%).

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Originally published in *Update in Anaesthesia*, edition 21 (2006) and reprinted from 'Continuing Education in Anaesthesia, Critical Care and Pain' by kind permission of the Board of Management and Trustees of the British Journal of Anaesthesia

Carbon Dioxide Transport

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INTRODUCTION

Carbon dioxide is produced by cell metabolism in the mitochondria. The amount produced depends on the rate of metabolism and the relative amounts of carbohydrate, fat and protein metabolized. The amount is about 200ml.min⁻¹ when at rest and eating a mixed diet; this utilizes 80% of the oxygen consumed, giving a respiratory quotient of 0.8 (respiratory quotient = rate of carbon dioxide production divided by rate of oxygen consumption). A carbohydrate diet gives a quotient of 1 and a fat diet 0.7.

CARBON DIOXIDE TRANSPORT IN THE BLOOD

Carbon dioxide is transported in the blood, from the tissues to the lungs in three ways: (i) dissolved in solution; (ii) buffered with water as carbonic acid; (iii) bound to proteins, particularly haemoglobin.

Approximately 75% of carbon dioxide is transported in the red blood cell and 25% in the plasma. The relatively small amount in plasma is attributable to a lack of carbonic anhydrase in plasma, so association with water is slow; plasma plays little role in buffering and combination with plasma proteins is poor.

There is a difference between the percentage of the total carbon dioxide carried in each form and the percentage exhaled from them. For example, 5% of the total is in solution but 10% of exhaled carbon dioxide comes from this source; 10% is protein bound, particularly with haemoglobin, but this supplies 30% of the exhaled amount.

Dissolved carbon dioxide

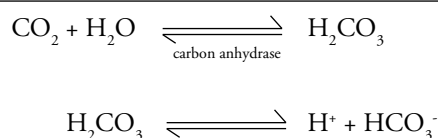
Carbon dioxide is 20 times more soluble than oxygen; it obeys Henry's law, which states that the number of molecules in solution is proportional to the partial pressure of the gas at the liquid surface. The carbon dioxide solubility coefficient is 0.0308mmol.l⁻¹.mmHg⁻¹ or 0.231mmol.l⁻¹.kPa⁻¹ at 37°C. Solubility increases as the temperature falls.

This corresponds to 0.5ml.kPa⁻¹ carbon dioxide in 100 ml blood at 37°C. The partial pressure of carbon dioxide is 5.3kPa in arterial blood and 6.1kPa in mixed venous blood; therefore, arterial blood will contain about 2.5ml per 100ml of dissolved carbon dioxide

and venous blood 3ml per 100ml. A cardiac output of 5l.min⁻¹ will carry 150ml of dissolved carbon dioxide to the lung, of which 25ml will be exhaled. Because of this high solubility and diffusion capacity, the partial pressure of carbon dioxide in alveolar and pulmonary end-capillary blood are virtually the same. Even a large shunt of 50% will only cause a end-pulmonary capillary/arterial carbon dioxide gradient of about 0.4kPa.

Carbonic acid

Carbon dioxide combines with water to form carbonic acid, a reaction accelerated by carbonic anhydrase. The carbonic acid then freely dissociates (Equation 1):



The enzyme carbonic anhydrase is present in a number of organs of the body including the eye, kidney and brain; however, for this purpose, it is the red blood cell carbonic anhydrase that is important. Once carbonic acid is formed it dissociates easily so that the ratio of H₂CO₃ to HCO₃⁻ is 1:20 (Equation 2).

$$\frac{\text{CO}_2}{\text{H}_2\text{CO}_3} = \frac{1000}{1} \quad \frac{\text{H}_2\text{CO}_3}{\text{HCO}_3^-} = \frac{1}{20}$$

Carbon dioxide and water diffuse freely into the red blood cell and are converted to carbonic acid, which dissociates into hydrogen and bicarbonate ions. Hydrogen ions do not pass through cell membranes but carbon dioxide passes readily. This situation cannot be sustained as the intracellular hydrogen ion and bicarbonate ion concentration, osmolarity and cell size will rise and rupture the cell. The bicarbonate ion diffuses out to the plasma to be exchanged for chloride ions. This is known as the **chloride shift** (Gibbs–Donnan equilibrium or Hamburger effect). An ion exchange transporter protein in the cell membrane called Band 3 for Cl⁻ and HCO₃⁻ facilitates chloride shift. A build up of hydrogen ion in the red blood cell would also prevent further conversion and production of bicarbonate ion.

Summary

Carbon dioxide is transported in the blood in three ways:

- (i) dissolved in solution;
- (ii) buffered with water as carbonic acid;
- (iii) bound to proteins, particularly haemoglobin.

At a haemoglobin concentration of 15g.dl⁻¹, and a mixed venous PCO₂ of 6.1kPa, venous blood contains 52ml.dl⁻¹ carbon dioxide; arterial blood with a PCO₂ of 5.3kPa contains 48ml.dl⁻¹. The effects of carbon dioxide production in the tissues include: increased plasma Cl⁻; increased red blood cell mean corpuscular volume; and haemoglobin becoming less acidotic than oxygenated haemoglobin.

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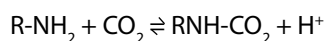
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However, hydrogen ions bind easily to reduced haemoglobin, which is made available when oxygen is released; therefore, free hydrogen ions are removed from solution. Reduced haemoglobin is less acidic than oxygenated haemoglobin. This is another way of stating the **Haldane effect**, which explains that, at any given $p\text{CO}_2$, the carbon dioxide content of deoxygenated blood is greater than that of oxygenated blood.

As a result of the shift of chloride ions into the red cell and the buffering of hydrogen ions onto reduced haemoglobin, the intercellular osmolarity increases slightly and water enters causing the cell to swell. This can be measured as an increase in mean corpuscular volume (MCV). The reverse process occurs as the red blood cell passes through the lung.

Bound to haemoglobin and other proteins

Carbon dioxide combines rapidly to the terminal uncharged amino groups (R-NH_2) to form carbamino compounds (Equation 3).



In most proteins, it is only the terminal amino acid group that combines with carbon dioxide. Haemoglobin is different when forming carbaminohaemoglobin. Reduced haemoglobin is the only effective protein buffer of hydrogen ion at physiological pH because of its high content of the amino acid histidine. Hydrogen ions attach to the imidazole group of the histidine. About 30% of exhaled carbon dioxide was transported combined with haemoglobin protein.

The amount of carbon dioxide held in blood in the carbamino form is small but it accounts a third of the difference between venous and arterial carbon dioxide content. The Haldane effect reflects the difference in carbon dioxide content between oxygenated and reduced haemoglobin at the same $p\text{CO}_2$. This effect is partly attributable to the ability of haemoglobin to buffer hydrogen ions and partly due to the fact that reduced haemoglobin is 3.5 times more effective in combining with carbon dioxide than oxyhaemoglobin.

Different haemoglobins vary in their affinity for carbon dioxide, carbon monoxide and oxygen. Carbon dioxide combines readily with haemoglobin to form a carbamino bond at a lower partial pressure than oxygen, but haemoglobin carries less than a quarter of the amount of carbon dioxide compared with oxygen. By contrast, foetal haemoglobin combines with oxygen at a lower partial pressure due to the replacement of the β -chain with γ -chains. Carbon monoxide has a greater affinity for haemoglobin and so displaces oxygen.

CARBON DIOXIDE TRANSPORT IN THE TISSUES

Carbon dioxide transport in the tissue is summarized in Figure 1. Carbon dioxide combines with water to form carbonic acid. This reaction is very slow in plasma but fast within the red blood cell owing to the presence of the enzyme carbonic anhydrase. Carbonic acid (H_2CO_3) dissociates into H^+ and HCO_3^- ions; therefore, the concentration of both H^+ and HCO_3^- is increased in the red blood cell. HCO_3^- can diffuse out of the red blood cell into plasma whereas H^+ cannot. In order to maintain electrical neutrality, chloride ions diffuse into the red blood cell from the plasma as HCO_3^- diffuses out. Hydrogen ions are taken up by reduced haemoglobin. The

imidazole group of the amino acid histidine gives haemoglobin a very significant buffering capacity, not present in other amino acids. This buffering capacity is made possible by the fact that each tetramer of haemoglobin contains 38 histidine residues and the dissociation constant of the imidazole groups of the four histidine residues, to which the haem groups are attached, is affected by the state of oxygenation of the haem. In the acidic state, the oxygen bond is weakened, while reduction of haemoglobin causes the imidazole group to become more basic. In the tissues, the acidic form of the imidazole group weakens the strength of the oxygen bond at the same time as hydrogen ions are being buffered by the more basic haemoglobin.

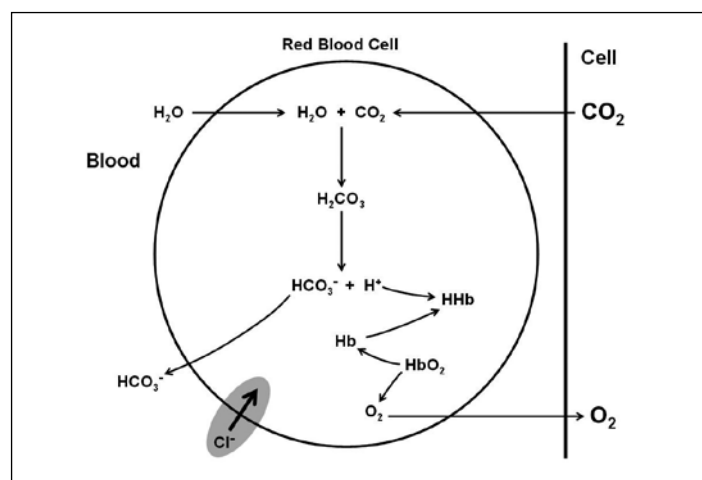
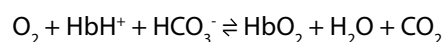


Figure 1. Movement of gases at tissue level with the chloride shift highlighted

CARBON DIOXIDE TRANSPORT IN THE LUNGS

The combination of oxygen with haemoglobin is facilitated by the histidine group becoming more basic, which increases the affinity of the haem group for oxygen as the carbon dioxide is lost (Equation 4). This is one reason for the **Bohr effect**.



Release of Hb shifts the equilibrium in favour of carbon dioxide formation and elimination. HCO_3^- concentration decreases as carbon dioxide is formed and eliminated (Figure 2).

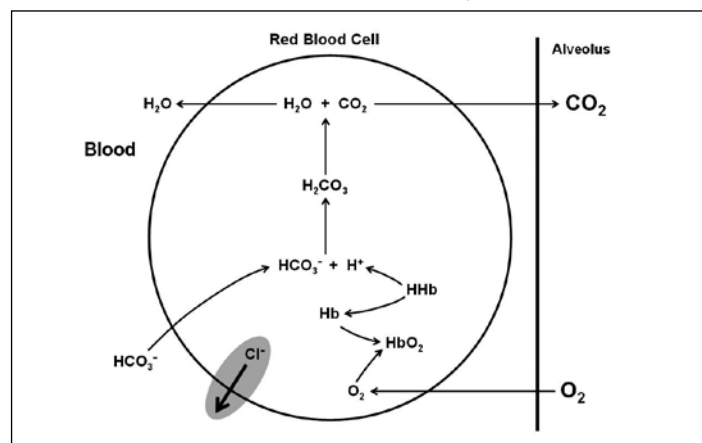


Figure 2. Movement of gases at alveolar level

CARBON DIOXIDE DISSOCIATION CURVES

Carbon dioxide dissociation curves relate PaCO_2 (kPa or mmHg) to the amount of carbon dioxide (ml) carried in blood (Figure 3). The amount of dissolved carbon dioxide and bicarbonate vary with pCO_2 , but are little affected by the state of haemoglobin. However, the amount of carbaminohaemoglobin is much affected by the state of oxygenation of haemoglobin, less so by the pCO_2 .

In mixed venous blood, PvCO_2 is 6.1 kPa (46 mmHg) and in arterial blood PaO_2 is 5.3 kPa (40 mmHg). Total carbon dioxide in venous

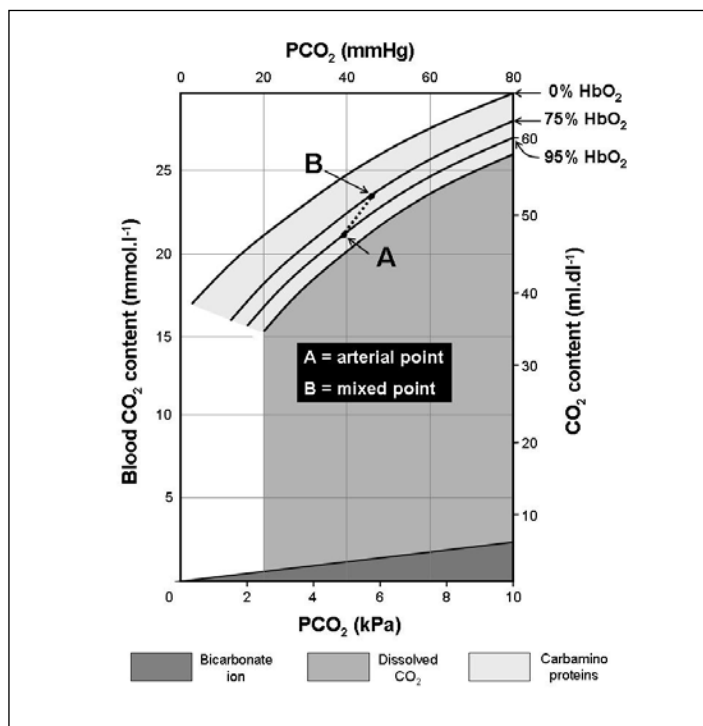


Figure 3. Total carbon dioxide transport in whole blood

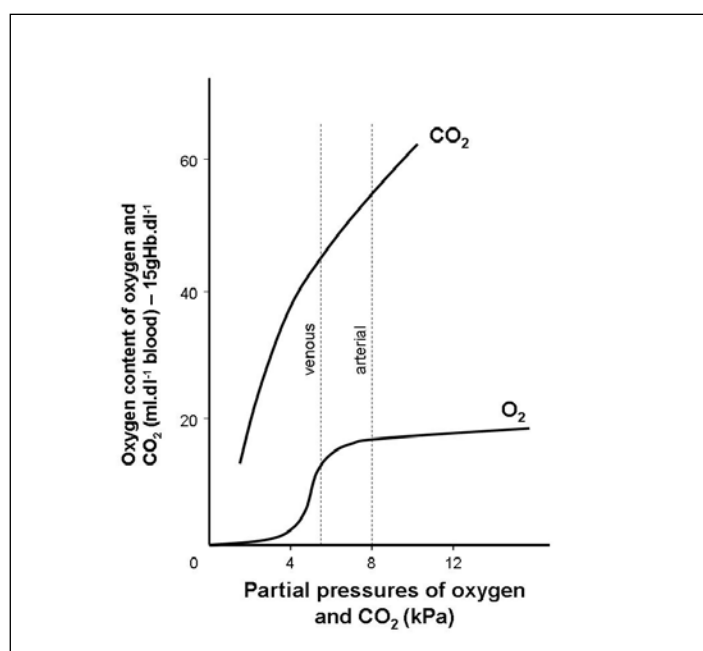


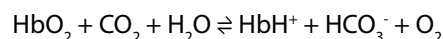
Figure 4. Partial pressure of oxygen and carbon dioxide

blood is 52 ml per 100 ml and in arterial blood 48 ml per 100 ml. Consequently, the curve is more linear than the O_2Hb dissociation curve.

Figure 4 illustrates the difference between the content in blood of oxygen and carbon dioxide with change in partial pressure. It emphasizes that the carbon dioxide content rises throughout the increase in partial pressure. Oxygen content rises more steeply until a point at which the haemoglobin is fully saturated. After that, the increase is small because of the small increased amount in solution.

DIFFERENCES BETWEEN VENOUS AND ARTERIAL BLOOD

The differences between arterial and venous blood are summarized in Figure 5. The high content of carbon dioxide in venous capillary blood reduces the affinity of haemoglobin for oxygen leading to release of oxygen to the tissues.¹ The oxygen dissociation curve shifts to the right (**Bohr effect**). Deoxygenated haemoglobin takes up more carbon dioxide than oxygenated haemoglobin (**Haldane effect**). Removal of oxygen from haemoglobin in the tissue capillaries causes the haemoglobin molecule to behave more like a base (better proton acceptor). Therefore, haemoglobin increases the amount of carbon dioxide that is carried in venous blood (Equation 4).



Each carbon dioxide molecule added to the red blood cell increases the intracellular osmotic pressure by an increase in either HCO_3^- or Cl^- ions. Therefore, the red blood cell increases in size and the haematocrit of venous blood is some 3% more than arterial blood. The plasma concentration of chloride ions is lower but bicarbonate ion concentration is greater.

pH OF RED BLOOD CELLS

The total reduction of all haemoglobin would result in a rise in blood pH by 0.03. At 25% oxygen saturation, the pH increases by 0.007 (at constant pCO_2). If the pCO_2 rises by 0.8 kPa (6 mmHg), i.e. the difference between mixed venous and arterial blood, the pH will reduce by 0.04. The net effect is a fall in pH of 0.033 from 7.4 to 7.36.

CHANGES IN RED BLOOD CELLS DURING PASSAGE THROUGH THE LUNGS

In pulmonary capillary blood, the red blood cell releases carbon dioxide and the haemoglobin affinity for oxygen is increased.

The oxygenated haemoglobin binds fewer hydrogen ions making it more acidic but the fall in pCO_2 , and the shift in chloride and bicarbonate ions, makes the red blood cell less acidic. The outward shift of water gives a smaller MCV and reduced haematocrit. The oxygen dissociation curve will shift to the left (Bohr effect). The plasma concentration of chloride ion is higher in arterial compared with venous blood; bicarbonate concentration is lower.

THE ROLE OF CARBON DIOXIDE IN ACID ELIMINATION

Every minute, 200 ml of carbon dioxide is exhaled; this is the equivalent to 12–13 mol of hydrogen ions in 24 h.² Urine pH varies from 4.5 to 8.0. A pH of 4.0 represents $10^{-4} \text{ mol.l}^{-1}$ of hydrogen ions. Therefore, the passage of 3 litres of urine accounts for a relatively small amount of hydrogen ion elimination in 24 hours; however, this

includes the phosphate and sulphate ions that cannot be converted to carbon dioxide.

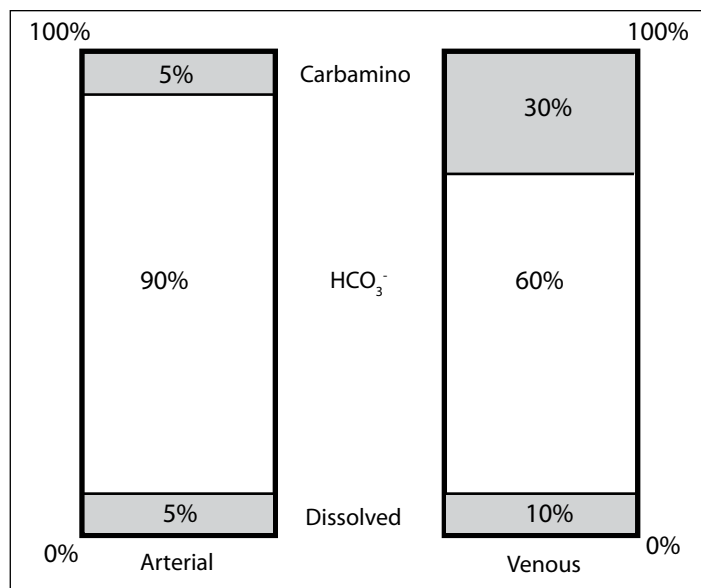


Figure 5. Distribution of carbon dioxide in arterial and venous blood

EFFECT OF APNOEA

The total body content of carbon dioxide including bicarbonate ion is 120 litres or 100 times that of oxygen. If there is apnoea and all the carbon dioxide is retained in the body, $p\text{CO}_2$ will rise by 0.4 to 0.8 kPa.min⁻¹ (3–6 mmHg.min⁻¹). Alveolar gas will rapidly equate with venous blood, giving an alveolar $p\text{CO}_2$ rise from 5.3 to 6.1 kPa and a $p\text{O}_2$ fall from 14 to 5.3 kPa in 1 minute. Therefore, the patient becomes rapidly hypoxaemic. If the patient is pre-oxygenated with oxygen 100%, the arterial oxygen tension will remain above 13 kPa and 100% saturation is maintained for several minutes as 250 ml.min⁻¹ of oxygen is used from a high partial pressure in the lung. However, PaCO_2 will steadily rise; after 5 min, it will be approaching 10 kPa with an associated fall in pH.

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Cerebral Blood Flow and Intracranial Pressure

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CEREBRAL BLOOD FLOW

The brain is unusual in that it is only able to withstand very short periods of lack of blood supply (ischaemia). This is because neurones produce energy (ATP) almost entirely by oxidative metabolism of substrates including glucose and ketone bodies, with very limited capacity for anaerobic metabolism. Without oxygen, energy-dependent processes cease, leading to irreversible cellular injury if blood flow is not re-established rapidly (3 to 8 minutes under most circumstances). Therefore, adequate cerebral blood flow must be maintained to ensure a constant delivery of oxygen and substrates, and to remove the waste products of metabolism.

Cerebral blood flow (CBF) is dependent on a number of factors that can broadly be divided into:

1. those affecting cerebral perfusion pressure
2. those affecting the radius of cerebral blood vessels

This relationship can be described by the Hagen-Poiseuille equation (see below) which describes the laminar flow of an incompressible uniformly viscous fluid (so called Newtonian fluid) through a cylindrical tube with constant circular cross-section. Although blood does not fulfill all of these criteria, it tends to flow in a laminar manner at the level of capillaries.

The Hagen-Poiseuille equation

$$\text{Cerebral Blood Flow} = \frac{\Delta P \pi R^4}{8 \eta l}$$

where: ΔP = cerebral perfusion pressure
 R = radius of the blood vessels
 η = viscosity of the fluid (blood)
 l = length of the tube (blood vessels)
 π = constant, 3.14

Some facts and figures

- CBF averages $50\text{ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$ (ranging from $20\text{ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$ in white matter to $70\text{ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$ in grey matter).
- The adult brain weighs 1400g or 2% of the total body weight. Therefore it can be seen that CBF is $700\text{ml} \cdot \text{min}^{-1}$ or 15% of the resting cardiac output.

- This reflects the high oxygen consumption of the brain of $3.3\text{ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$ ($50\text{ml} \cdot \text{min}^{-1}$ in total) which is 20% of the total body consumption. This is often referred to as the cerebral metabolic rate for oxygen or CMRO_2 . This is higher in the cortical grey matter and generally parallels cortical electrical activity.

CEREBRAL PERFUSION PRESSURE

Perfusion of the brain is dependent on the pressure gradient between the arteries and the veins and this is termed the cerebral perfusion pressure (CPP). This is the difference between the mean arterial blood pressure (MAP) and the mean cerebral venous pressure.

The latter is difficult to measure and approximates to the more easily measured intracranial pressure (ICP).

$$\text{CPP} = \text{MAP} - \text{ICP}$$

MAP can be estimated as equal to: diastolic blood pressure + $1/3$ pulse pressure (difference between systolic and diastolic pressures) and is usually around 90mmHg. ICP is much lower and is normally less than 13mmHg.

CPP is normally about 80mmHg

Clearly, CPP will be affected by anything that changes the MAP or ICP. Blood loss causing hypotension will reduce MAP and CPP (hence the reduced level of consciousness seen in severely shocked patients), while an intracerebral haematoma will increase ICP, with the same effect (see below for more details). Clearly if both co-exist, the effect is a catastrophic fall in CPP and the risk of brain ischaemia. An increase in CPP is usually the result of an increase in MAP, the contribution made by reducing ICP is minimal, except in pathological states when ICP is very high. In a normal brain, despite the potential for changes in MAP (sleep, exercise etc), CBF remains constant over a wide range of CPPs. This is achieved by a process called autoregulation (see below).

REGULATION OF CEREBRAL ARTERIAL BLOOD VESSEL CALIBRE

This is regulated by four primary factors:

Summary

The normal adult skull can be considered as a bony box of fixed volume, containing brain, blood and cerebrospinal fluid (CSF). An understanding of how these components interact is essential in managing normal patients under anaesthesia and those with intracranial pathology. These factors will be considered in two sections - cerebral blood flow and intracranial pressure.

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1. Cerebral metabolism
2. Carbon dioxide and oxygen levels
3. Autoregulation
4. Neurohumeral factors.

The radius of the arterial vessels is particularly important because, due to its effect on CBF, an increased radius (vasodilatation) leads to an increase in cerebral blood volume which in turn increases ICP and reduces CPP, so a balance must be reached.

Cerebral metabolism

Changes in CBF and metabolism tend to follow each other; local or global increases in metabolic demand are met rapidly by an increase in CBF and substrate delivery and vice versa (often referred to as flow-metabolism coupling, Figure 1). These changes are thought to be controlled by several vasoactive metabolic mediators including hydrogen ions, potassium, CO_2 , adenosine, glycolytic intermediates, phospholipid metabolites and more recently, nitric oxide (NO).

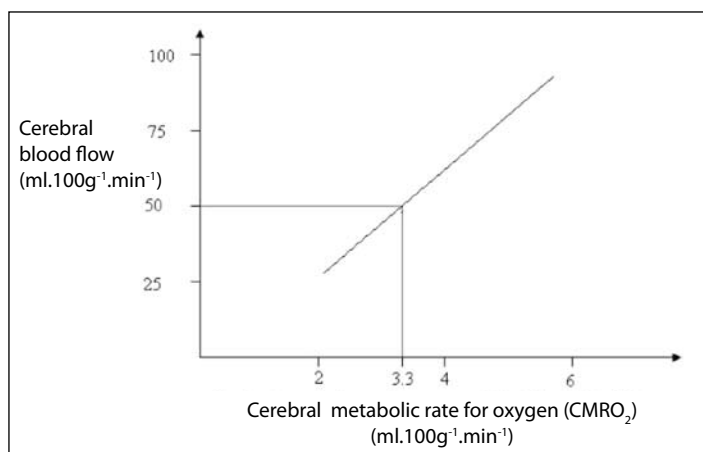


Figure 1. Graph illustrating coupling between CBF and CMRO_2 . Corresponding normal CBF and CMRO_2 values are represented by the grey line

Carbon dioxide and oxygen levels

At normotension, the relationship between partial pressure of carbon dioxide in arterial blood (PaCO_2) and CBF is almost linear and at a PaCO_2 of 10.6kPa (80mmHg) CBF is approximately doubled. No further increase in flow is possible at this point as the arterioles are maximally dilated. Conversely at 2.7kPa (20mmHg) flow is almost halved and again cannot fall further as the arterioles are maximally vasoconstricted (Figure 2). These effects are regulated by a complex and interrelated system of mediators. The initial stimulus is a decrease in brain extracellular pH brought about by an increase in PaCO_2 , further mediated by nitric oxide, prostanoids, cyclic nucleotides, potassium channels, and a decrease in intracellular calcium concentration as a final common mediator.

Arteriolar tone has an important influence on how PaCO_2 affects CBF. Moderate hypotension impairs the response of the cerebral circulation to changes in PaCO_2 , and severe hypotension abolishes it altogether.

The response of the cerebral vessels to CO_2 can be utilised to help manage patients with raised intracranial pressure, for example after

traumatic brain injury. Hyperventilation reduces the PaCO_2 and causes vasoconstriction of the cerebral vessels (reduces their radius) and therefore reduces cerebral blood volume and ICP. However if PaCO_2 is reduced too much, the resulting vasoconstriction can reduce CBF to the point of causing or worsening cerebral ischaemia. Clearly hypercapnia and the resulting vasodilatation and increase in ICP must also be avoided. PaCO_2 is therefore best maintained at low-normal levels to prevent raising ICP (35-40mmHg, 4.7-5.3kPa). This CO_2 reactivity may be lost in areas of the brain that are injured. Furthermore, impaired cerebral CO_2 vasoreactivity is associated with a poor outcome in patients with severe head injury. CO_2 reactivity is generally preserved during inhalation anaesthesia (up to about 1 MAC of volatile) and can therefore be utilised to help control ICP and brain swelling during surgery.

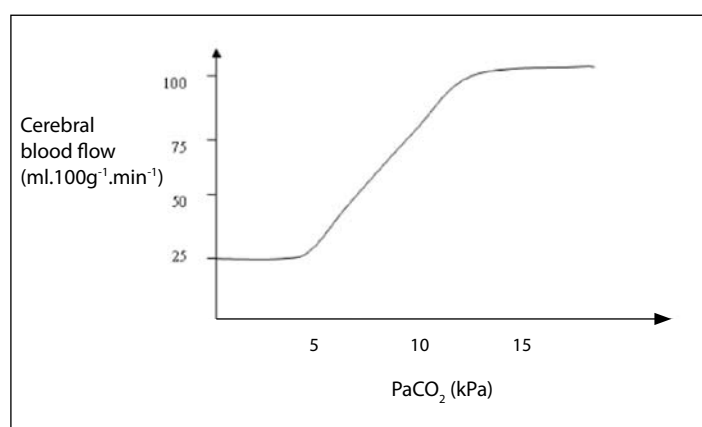


Figure 2. Relationship between CBF and PaCO_2

Oxygen has little effect on the radius of blood vessels at partial pressures used clinically (Figure 3).

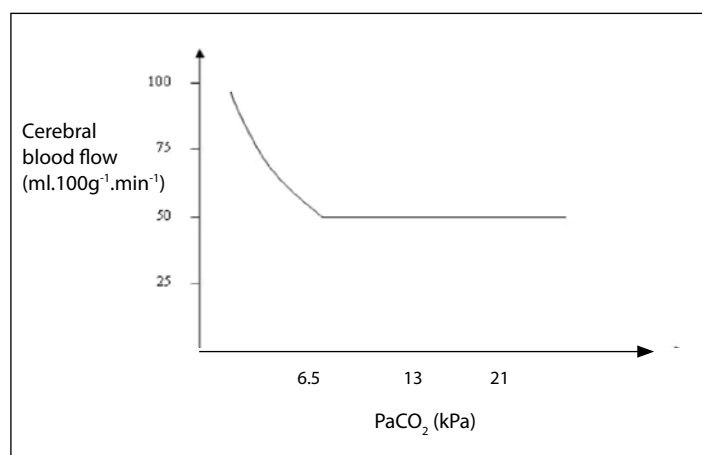


Figure 3. Relationship between CBF and PaO_2 showing little effect on CBF in the normoxaemic range. CBF increases if PaO_2 is less than 6.6kPa

CBF increases once PaO_2 drops below about 6.7kPa so that cerebral oxygen delivery remains constant. Hypoxia acts directly on cerebral tissue to promote the release of adenosine, and in some cases prostanoids that contribute significantly to cerebral vasodilatation. Hypoxia also acts directly on cerebrovascular smooth muscle to produce hyperpolarisation and reduce calcium uptake, both mechanisms enhancing vasodilatation.

Autoregulation

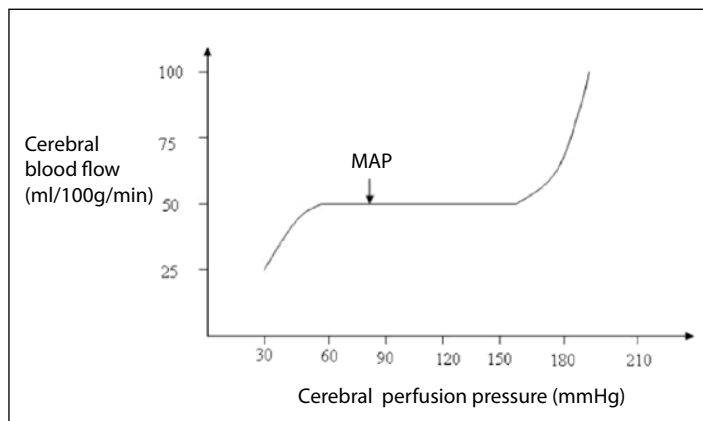


Figure 4. Relationship between cerebral blood flow and cerebral perfusion pressure. In chronic hypertension, the curve is shifted to the right

The brain requires a constant flow of blood over a range of pressures and this is achieved by the process of autoregulation. The stimulus to autoregulation is CPP, not MAP. In adults, under normal circumstances (ICP <10mmHg), CPP and MAP are very similar and CBF remains constant with a CPP of 60-160mmHg (Figure 4). The higher the ICP the more CPP deviates from MAP and must be calculated. The autoregulation curve is shifted to the right in chronic hypertensive patients and to the left in neonates and younger children, gradually moving to adult values as they get older.

Autoregulation is thought to be a myogenic mechanism, whereby vascular smooth muscle constricts in response to an increase in wall tension and to relax to a decrease in wall tension. At the lower limit of autoregulation, cerebral vasodilation is maximal, and below this level the vessels collapse and CBF falls passively with falls in MAP. At the upper limit, vasoconstriction is maximal and beyond this the elevated intraluminal pressure may force the vessels to dilate, leading to an increase in CBF and damage to the blood-brain-barrier. Metabolic mediators, such as adenosine, may also be involved in the low-pressure range of autoregulation. As with all the other mechanisms that affect the radius of the blood vessels, autoregulation will also change the cerebral blood volume and may affect ICP.

Pressure autoregulation can be impaired in many pathological conditions including patients with a brain tumour, subarachnoid haemorrhage, stroke, or head injury. A loss of CBF regulatory capacity can be attributed either to damage of the control system (eg. cerebral vessels) or of the feedback mechanisms involved in the brain's haemodynamic control. At this time, CBF becomes pressure-dependent and thus small changes in MAP can have profound changes on CBF and cerebral blood volume.

Neurohumoral factors

A major difference between other systemic circulations and the cerebral circulation is the relative lack of humoral and autonomic control on normal cerebrovascular tone. The main action of the sympathetic nerves is vasoconstriction that protects the brain by shifting the autoregulation curve to the right in hypertension. The parasympathetic nerves contribute to vasodilatation and may play a part in hypotension and reperfusion injury (for example after cardiac arrest).

Other factors

Blood viscosity

This is directly related to haematocrit. As viscosity falls, CBF increases (see Hagen-Poiseuille equation). However, there will also be a reduction in oxygen-carrying capacity of the blood. The optimal haematocrit is where there is a balance between flow and capacity, usually about 30%.

Temperature

CMRO₂ decreases by 7% for each 1°C fall in body temperature and is paralleled by a similar reduction in CBF. At 27°C, CBF is approximately 50% of normal. By 20°C, CBF is about 10% of normal. The reduction in CMRO₂ is the factor that allows cold patients to withstand prolonged periods of reduced CBF without ischaemic damage for example during cardiopulmonary bypass. Again, because of vasoconstriction, cerebral blood volume and ICP are reduced. Although this has been tried to help control high ICP, clinical trials have been disappointingly ineffective in showing an improved outcome.

Drugs

Cerebral metabolism can be manipulated (reduced) and consequently CBF, cerebral blood volume and ICP is reduced. Infusions of the barbiturate thiopentone have been used to help control high ICP after head injury, however there is little convincing evidence of benefit.

Anaesthetic drugs have a significant effect on cerebral blood vessels; volatile agents cause a reduction in the tension of cerebral vascular smooth muscle resulting in vasodilatation and an increase in CBF. Interestingly many of the newer drugs (isoflurane, sevoflurane) also reduce neuronal function and metabolic demands, and as a result this can lead to uncoupling of flow-metabolism. This appears to be dependent on the concentration of volatile anaesthetic given. The vasodilatation can be countered by mild hyperventilation to a PaCO₂ at the low end of the normal range (4.0-4.5kPa), without serious risk of cerebral ischaemia.

INTRACRANIAL PRESSURE (ICP)

Intracranial pressure is important as it affects cerebral perfusion pressure and cerebral blood flow. Normal ICP is between 5 and 13mmHg. Because it is very dependant on posture, the external auditory meatus is usually used as the zero point.

Some facts and figures

- Constituents within the skull include the brain (80%, 1400ml), blood (10%, 150ml) and cerebrospinal fluid (CSF 10%, 150ml).
- The skull is a rigid box, so if one of the three components increases in volume then there must be compensation by a decrease in the volume of one or more of the remaining components otherwise the ICP will increase (Figure 5). The term compliance is often used to describe this relationship, but it is more accurately **elastance**, the reciprocal of compliance (change in pressure for unit change in volume).
- Compensatory mechanisms include movement of CSF into the spinal sac, increased reuptake of CSF and compression of venous sinuses. These mechanisms reduce the liquid volume of the intracranial contents.

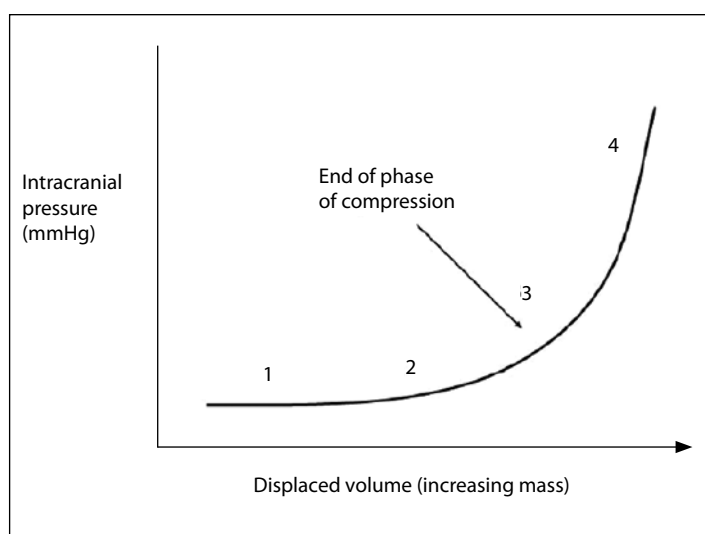


Figure 5. ICP elastance curve (change in pressure per unit change in volume)

Stage 1/2 = compensation phase. As one of the intracranial constituents increases in volume, the other two constituents decrease in volume in order to keep the intracranial pressure constant.

Stage 3/4 = decompensated phase. When compensatory mechanisms are exhausted, small increases in the volumes of intracranial constituents cause large increases in ICP.

The slope of the curve is dependent on which intracranial constituent is increasing. If it is blood or CSF, both of which are poorly compressible, then the slope is steeper. If it is brain tissue, such as a tumour or oedema, the curve is less steep as the tissue is compressible.

CEREBROSPINAL FLUID (CSF)

CSF is a specialised extracellular fluid in the ventricles and subarachnoid space which has a multitude of functions.

Functions of the CSF

- Mechanical protection by buoyancy. The low specific gravity of CSF (1.007) reduces the effective weight of the brain from 1.4kg to 47g (Archimede's principle). This reduction in mass reduces brain inertia and thereby protects it against deformation caused by acceleration or deceleration forces.

- CSF provides a constant chemical environment for neuronal activity.
- CSF is important for acid-base regulation for control of respiration.
- CSF provides a medium for nutrients after they are transported actively across the blood-brain-barrier.

CSF is produced at a rate of $0.3-0.4\text{ml}\cdot\text{min}^{-1}$ ($500\text{ml}\cdot\text{day}^{-1}$) by the choroid plexus in the lateral, third and fourth ventricles. CSF is produced by the filtration of plasma through fenestrated capillaries followed by active transport of water and dissolved substances through the epithelial cells of the blood-CSF barrier. This is distinct from the blood-brain-barrier which consists of endothelial cells linked by tight junctions whose function is to protect the brain from chemicals in the blood stream. CSF formation is dependent on the CPP and when this falls below 70mmHg, CSF production also falls because of the reduction in cerebral and choroid plexus blood flow.

Following production, CSF then circulates through the ventricular system and the subarachnoid spaces, aided by ciliary movements of the ependymal cells. Resorption takes place mostly in the arachnoid villi and granulations into the circulation: the mechanism behind the resorption is the difference between the CSF pressure and the venous pressure. An obstruction in CSF circulation, overproduction of CSF or inadequate resorption results in hydrocephalus.

PATHOLOGICAL CONDITIONS CAUSING A RISE IN VOLUME OF INTRACRANIAL CONSTITUENTS

Any of the three intracranial constituents (tissue, blood or CSF) can increase in size and volume (Table 2).

EFFECTS OF A RAISED ICP

As ICP rises, CPP falls eventually to a point when there is no cerebral blood flow, no cerebral perfusion and brain death. Prior to this, brain structures begin to herniate (protrude through an opening).

Physiological compensatory mechanisms occur to try and maintain cerebral blood flow:

- **Temporal lobe herniation** beneath the tentorium cerebelli (uncal herniation) – causes cranial nerve III palsy (dilatation of pupil on the same side as lesion (ipsilateral) followed by movement of eye down and out).

Table 1. Comparison of the compositions of CSF and plasma

	Plasma (mmol.l ⁻¹)	CSF (mmol.l ⁻¹)
Urea	2.5-6.5	2.0-7.0
Glucose (fasting)	3.0-5.0	2.5-4.5
Sodium	136-148	144-152
Potassium	3.8-5.0	2.0-3.0
Calcium	2.2-2.6	1.1-1.3
Chloride	95-105	123-128
Bicarbonate	24-32	24-32
Protein	60-80g.l ⁻¹	200-400mg.l ⁻¹

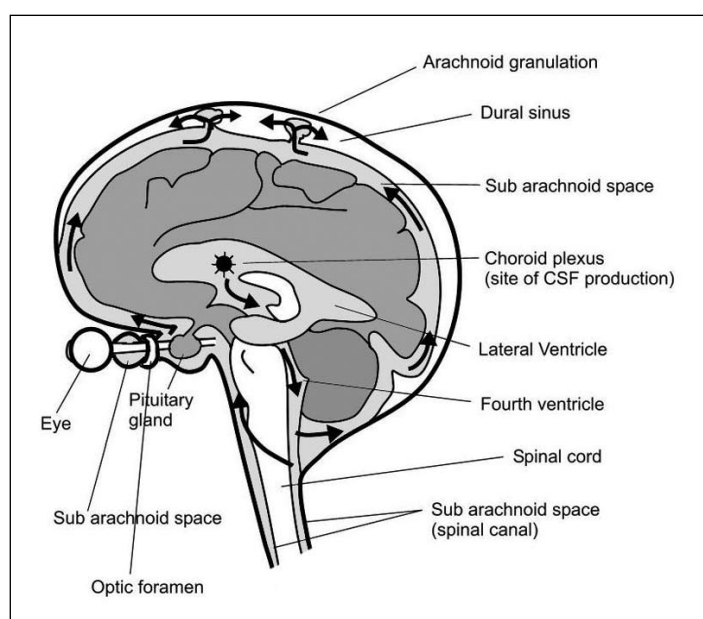


Figure 6. Production, circulation and resorption of CSF. Production mostly takes place in the choroid plexus of the lateral ventricles. CSF circulates to the subarachnoid spaces, where resorption takes place via the arachnoid granulations and villi. When ICP is raised, the pressure is transmitted along the optic nerve causing papilloedema

- **Herniation of cerebellar peduncles** through the foramen magnum (tonsillar herniation). Pressure on the brainstem causes the Cushing reflex – hypertension, bradycardia and Cheyne-Stokes respiration (periodic breathing).
- **Subfalcine herniation** occurs when the cingulate gyrus on the medial aspect of the frontal lobe is displaced across the midline under the free edge of the falx cerebri and may compress the anterior cerebral artery.
- **Upward or cerebellar herniation** occurs with either a large mass or increased pressure in the posterior fossa. The cerebellum is displaced in an upward direction through the tentorial opening and causes significant upper brainstem compression.

HOW CAN ICP BE INFLUENCED?

Primary brain damage occurs at the time of a head injury and is

unavoidable except through preventative measures. The aim of management following this is to reduce secondary brain damage which is caused by a reduction in oxygen delivery due to hypoxaemia (low arterial PaO_2) or anaemia, a reduction in cerebral blood flow due to hypotension or reduced cardiac output, and factors which cause a raised ICP and reduced CPP.

The most important management strategy ensures A (Airway and C spine protection in trauma), B (Breathing and adequate oxygenation) and C (blood pressure and CPP). Following this, further strategies to reduce ICP and preserve cerebral perfusion are required. Techniques that can be employed to reduce ICP are aimed at reducing the volume of one or more of the contents of the skull (Table 3).

Often, blood pressure needs to be augmented with drugs that produce arterial vasoconstriction such as metaraminol or norepinephrine (which requires central venous access). Following a head injury when autoregulation is impaired, if there is a drop in MAP from drugs or blood loss, the resulting cerebral vasodilatation increases cerebral blood volume, which in turn raises ICP and further drops CPP. This starts a vicious cycle. So by raising MAP, ICP can often be reduced.

MEASURING ICP

ICP is traditionally measured by use of a ventriculostomy or external ventricular drain (EVD), which involves a catheter that is placed through a small hole in the skull (burr hole) into the lateral ventricle. ICP is then measured by transducing the pressure in a fluid column. Ventriculostomies also allow drainage of CSF, which can be effective in decreasing the ICP. More commonly ICP is now measured by placing some form of measuring device (for example a miniature transducer) within the brain tissue (intraparenchymal monitor). An epidural monitor can also be used but becomes increasingly unreliable at extremes of pressure.

The normal ICP waveform is a triphasic wave, in which the first peak is the largest peak and the second and third peaks are progressively smaller. When intracranial compliance is abnormal, the second and third peaks are usually larger than the first peak. In addition, when intracranial compliance is abnormal and ICP is elevated, pathological waves may appear. Lundberg described 3 types of abnormal ICP waves in 1960, that he named A, B, and C waves. Although these can be identified, it is more common nowadays to measure the mean ICP and use this to calculate CPP.

Table 2. Conditions causing raised ICP

Brain Tissue	Blood	CSF
Tumours	Intracerebral, subarachnoid, subdural, extradural haematomas	Hydrocephalus
Cerebral oedema secondary to trauma, infection, infarction, hyponatraemia, hypertensive encephalopathy, acute liver failure, Reye's syndrome	Arteriolar dilatation secondary to hypoxaemia, hypercarbia, anaesthetic drugs, hyperthermia, seizures, hypotension	Meningeal diseases Choroid plexus tumour
Cerebral abscess	Venous dilatation secondary to venous obstruction from high PEEP, coughing, straining, heart failure, venous sinus thrombosis, head-down tilt, tight neck ties	
Cerebral contusions		

Table 3. *Strategies to reduce ICP*

Reduce brain tissue volume	Reduce blood volume	Reduce CSF volume
Tumour resection, abcess drainage	Evacuation of haematomas	Insertion of external ventricular drain or ventriculoperitoneal shunt to reduce CSF volume reduce (more long term measure)
Steroids (especially dexamethasone) to reduce cerebral oedema	Arterial: avoiding hypoxaemia, hypercarbia, hyperthermia, vasodilatory drugs, hypotension	
Mannitol/furosemide to reduce intracellular volume	Barbiturate coma to reduce CMRO ₂ and cerebral blood volume	
Hypertonic saline to reduce intracellular volume	Venous: patient positioning with 30° head up, avoiding neck compression with ties/excessive rotation, avoiding PEEP/airway obstruction/CVP lines in neck	
Decompressive craniectomy to increase intracranial volume		

If ICP is not measured directly, we can estimate it and therefore make changes in MAP to maintain CPP:

- Patient drowsy and confused (GCS 9-13) ICP ~20mmHg
- GCS ≤ 8, ICP ~ 30mmHg

MEASURING THE ADEQUACY OF CEREBRAL PERFUSION

This is difficult as ideally adequacy of cerebral perfusion would be determined at a cellular level to determine whether neurones are receiving adequate oxygen and nutrients. Inferences about cerebral perfusion can be made by looking at a variety of measured variables. The first five techniques can be used at the bedside and are often part of multimodal monitoring of head injured patients. The latter techniques are more invasive and generally restricted to research programs.

- Measuring ICP and calculating CPP (most common method).
- Jugular venous bulb oxygen saturations (SjvO₂, usually 65-75%). Reflects the balance between cerebral oxygen delivery and CMRO₂. A low SjvO₂ reliably indicates cerebral hypoperfusion.
- Transcranial Doppler to measure blood velocity and estimate CBF.

- Microdialysis catheters to measure glucose, pyruvate, lactate, glycerol, glutamate (metabolic variables).
- Positron Emission Tomography – the distribution of radiolabelled water in the brain is monitored to indicate metabolic activity.
- Functional MR imaging techniques.
- Kety-Schmidt equation to determine CBF by using an inert carrier gas (using ¹³³Xe).
- Near infrared spectroscopy (NIRS) to measure oxygenation in a localised cerebral field.

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The Autonomic Nervous System - Basic Anatomy and Physiology

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INTRODUCTION

Many bodily functions proceed without any conscious supervision from our central nervous system (CNS). For example, we don't have to remember to digest our food after a meal, or sweat when too warm. These functions are controlled subconsciously, with a degree of automaticity, by a branch of the nervous system - the autonomic nervous system (ANS). The ANS is instrumental in the control of most of the body's organ systems, via a series of neural reflexes. The afferent limb of these reflexes can be from the peripheral or central nervous system. The efferent limb is mediated by the sympathetic or parasympathetic divisions of the ANS, which are functionally and structurally distinct. The observed physiological effect of the ANS depends upon several neurotransmitter and receptor types and so there are many targets for pharmacological manipulation.

AFFERENT PATHWAYS

Although the ANS is predominantly an efferent system, transmitting impulses from the central nervous system (CNS) to peripheral organ systems, it receives afferent inputs (i.e. transmit information from the periphery to the CNS) into its reflex arcs from:

The ANS itself

These afferent neurones are concerned with the mediation of visceral sensation and the regulation of vasomotor and respiratory reflexes. Examples are the baroreceptors and chemoreceptors in the carotid sinus and aortic arch, which are important in the control of heart rate, blood pressure and respiratory activity. The afferent fibres are usually carried to the CNS by major autonomic nerves such as the vagus, splanchnic or pelvic nerves, although afferent pain fibres from blood vessels may be carried by somatic nerves.

Other parts of the CNS

An example is the 'vaso-vagal response' to impending cannulation in a needle-phobic patient.

EFFERENT PATHWAYS

The efferent limb of neuronal autonomic reflexes consists of specific primary autonomic nerves (preganglionic nerves) that synapse in autonomic

ganglia, with secondary or postganglionic fibres. These postganglionic fibres mediate the desired response at the effector organ. The efferent limbs of these reflexes may also involve the somatic nervous system (e.g. coughing and vomiting). Simple reflexes are completed entirely within the organ concerned, whereas more complex reflexes are controlled by the higher autonomic centres in the CNS, principally the hypothalamus.

The effector limb of the ANS is subdivided into two separate divisions on the basis of anatomical and functional differences - the **sympathetic** and **parasympathetic** nervous systems. These two divisions differ in both structure and function.

In general the sympathetic nervous system can be thought of as preparing the body for 'fight or flight'. In the cardiovascular system, increased inotropic and chronotropic drive lead to increased cardiac output and blood flow is routed toward vital organs and skeletal muscle. There is an overall increase in CNS stimulation and respiratory drive is increased. Visceral activity is decreased.

The parasympathetic nervous system in contrast, increases the activity of the abdominal viscera. The cardiovascular system is depressed - reducing heart rate and cardiac output, and routing blood flow toward visceral beds. The respiratory system and CNS are also depressed.

STRUCTURE OF THE AUTONOMIC NERVOUS SYSTEM

Both the sympathetic and parasympathetic systems consist of myelinated preganglionic fibres that make synaptic connections with unmyelinated postganglionic fibres, and it is these which then innervate the effector organ. These synapses usually occur in clusters called **ganglia**. Most organs are innervated by fibres from both divisions of the ANS, and the influence is usually opposing, for example the vagus slows the heart, whilst the sympathetic nerves increase its rate and contractility. The effects on some organs, such as the salivary glands may be in parallel.

Sympathetic nervous system

In addition to its close functional relationship to the

Summary

The ANS can be thought of as the regulatory system that partly or wholly controls most of the body's organ systems and homeostatic mechanisms. In general, ANS effects are involuntary, relatively rapid, neuronal reflexes. ANS effects include control of heart rate and force of contraction, constriction and dilatation of blood vessels, contraction and relaxation of smooth muscle in various organs, visual accommodation, pupillary size and secretions from exocrine and endocrine glands.

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central nervous system, the ANS shares a close anatomical proximity. In the sympathetic nervous system, the ganglia are fused to form the sympathetic chain, which lies adjacent to the spinal column throughout most of its length. Preganglionic sympathetic fibres have cell bodies in the intermediolateral column (lateral horn) of grey matter in the spinal cord between the first thoracic and second lumbar vertebrae (T1 to L2). These fibres emerge from the spinal cord and travel a short distance in the primary ventral rami of a mixed spinal nerve (anterior nerve root) and pass to the sympathetic ganglia via the white rami communicantes (Figure 1). The ganglia are mainly arranged in two paravertebral chains (the sympathetic ganglionic chains) which lie anterolateral to the vertebral bodies and extend from the cervical to the sacral region. In the sympathetic chain the fibres will synapse, giving rise to unmyelinated postganglionic fibres that rejoin the spinal nerves via the grey rami communicantes and are conveyed to the effector organ. Some preganglionic fibres however ascend or descend to other levels of the sympathetic chain prior to synapsing (5 in Figure 1). In general therefore, sympathetic preganglionic fibres are short, and postganglionic fibres tend to be longer.

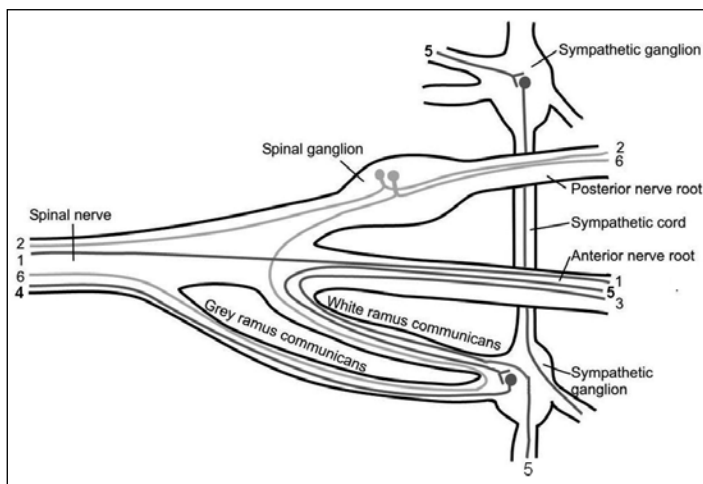


Figure 1. The anatomy of the sympathetic nervous system at the spinal level. The numbered nerves are: 1. somatic efferent; 2. somatic afferent; 3. sympathetic efferent (preganglionic) synapsing with 4. sympathetic efferent (postganglionic); 5. sympathetic efferent passing descending to a lower level in the sympathetic chain; 6. sympathetic afferent

Parasympathetic nervous system

Parasympathetic preganglionic fibres leave the CNS in both cranial and sacral nerves. Cranial fibres arise from specific parasympathetic brainstem motor nuclei of cranial nerves III (oculomotor nerve), VII (facial nerve), IX (glossopharyngeal nerve), and X (vagus nerve). The fibres travel with the main body of fibres within the cranial nerves to ganglia that tend to be distant from the CNS and close to the target organ. The ganglion cells may be either well organised (e.g. myenteric plexus of the intestine) or diffuse (e.g. bladder, blood vessels). In contrast to the sympathetic nervous system, the preganglionic fibres tend to be long, whereas the postganglionic fibres are shorter.

Sacral preganglionic fibres emerge from the CNS via the ventral rami of nerves S2 to S4 and form the pelvic splanchnic nerves, which pass to ganglia close to the effector organs.

The cranial nerves III, VII and IX affect the pupil and salivary gland secretion, whilst the vagus nerve (X) carries fibres to the heart, lungs, stomach, upper intestine and ureter. The sacral fibres form pelvic plexuses which innervate the distal colon, rectum, bladder and reproductive organs.

The basic structure of the ANS is illustrated in Figure 2.

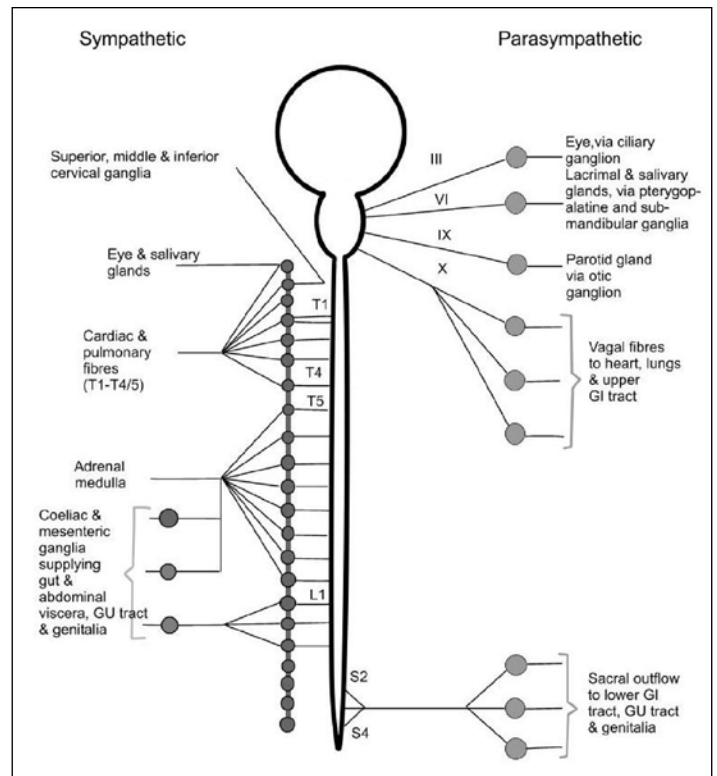


Figure 2. The anatomy of the autonomic nervous system

The anatomical differences between the two divisions of the ANS have great clinical relevance, particularly to anaesthetists. Anaesthetic interventions may have a greater or lesser effect on the sympathetic or parasympathetic nerves. A good example of this can be seen during spinal anaesthesia. A spinal block will temporarily halt input to the sympathetic afferents at the affected levels, leading to vasodilatation and loss of sweating in the affected dermatomes. If the block is allowed to spread to the levels supplying cardiac sympathetic fibres (T1 to T4), there will be a loss of both inotropic and chronotropic drive to the heart, reducing the cardiac output and causing progressive hypotension. The parasympathetic supply to the heart, travelling in the vagus nerve will be unaffected by the spinal block, leading to unopposed parasympathetic stimulation and bradycardia.

THE PHYSIOLOGY OF THE ANS

In order to understand the functions of the ANS, and the possible targets for pharmacological manipulation, it is necessary to have a basic knowledge of the neurotransmitters and receptors that are integral to the ANS.

As with all neuronal systems, the effects of the ANS are mediated by the release of neurotransmitters. Preganglionic fibres of both the sympathetic and parasympathetic nervous systems secrete acetylcholine, with nicotinic receptors (see below) predominating

in autonomic ganglia. Sympathetic postganglionic fibres are mostly adrenergic in nature – they secrete norepinephrine and occasionally epinephrine. Epinephrine and norepinephrine are both catecholamines, and are both synthesized from the essential amino acid phenylalanine by a series of steps, which includes the production of dopamine. The effect of postganglionic nerve stimulation depends upon the receptors present at the effector site – usually α - or β -adrenoreceptors. The effects are terminated by norepinephrine re-uptake into the presynaptic nerve ending where it is inactivated by the enzyme Monoamine Oxidase in mitochondria or metabolism locally by the enzyme Catechol-O-Methyl-Transferase.

A special case within the sympathetic nervous system is the nerve to the adrenal medulla. The adrenal medulla responds to nervous impulses in the sympathetic cholinergic preganglionic fibres by transforming the neural impulses into hormonal secretion. This nerve does not synapse within the sympathetic chain and hence is strictly still preganglionic when it reaches the adrenal medulla and consequently secretes acetylcholine as its neurotransmitter. The cells of the adrenal medulla can be thought of as a modified autonomic ganglion, but due to the presence of an additional enzyme the majority of norepinephrine is converted to epinephrine. In situations involving physical or psychological stress, much larger quantities are released.

Parasympathetic postganglionic fibres release acetylcholine. Most effects are mediated via muscarinic receptors and actions are terminated when acetylcholine is hydrolysed by acetylcholinesterase within the synaptic cleft.

Neurotransmitters bind with specific receptors at target cells to produce their effects. Different receptor subtypes exist in each of the divisions of the ANS, and the intracellular response in the target cell and hence the target organ, is specific to the receptor type.

Within the sympathetic nervous system, effects are generally mediated by adrenoreceptors. In the parasympathetic system effects are mediated generally by muscarinic acetylcholine receptors. A further exception to this rule is the sympathetic postganglionic fibres supplying sweat glands. These fibres secrete acetylcholine and exert their effects via muscarinic receptors.

ADRENORECEPTORS

Adrenoreceptors are subdivided into α - and β -receptors. Each of these classes is further divided into subgroups – α_1 and α_2 , β_1 , β_2 and β_3 .

α -receptors

α -receptors are G-protein linked receptors. They act via the G-protein subgroup G_z and phospholipase C to increase cytoplasmic calcium

Table 1. Summary of the effects of the autonomic nervous system at different organs

Organ	Sympathetic stimulation	Parasympathetic stimulation
Heart	↑ heart rate (β_1 (and β_2) ↑ force of contraction β_1 (and β_2) ↓ conduction velocity	↓ heart rate ↓ force of contraction ↑ conduction velocity
Arteries	constriction (α_1) dilatation (β_2)	dilatation
Veins	constriction (α_1) dilatation (β_2)	
Lung	bronchial muscle relaxation (β_2)	bronchial muscle contraction ↑ bronchial gland secretions
Gastrointestinal tract	↓ motility (β_2) contraction of sphincters (α)	↑ motility relaxation of sphincters
Liver	glycogenolysis (β_2 and α) gluconeogenesis (β_2 and α) lipolysis (β_2 and α)	glycogen synthesis
Kidney	renin secretion (β_2)	
Bladder	detrusor relaxation (β_2) contraction of sphincter (α)	detrusor contraction relaxation of sphincter
Uterus	contraction of pregnant uterus (α) relaxation of pregnant and non-pregnant uterus (β_2)	
Eye	dilates pupil (α)	constricts pupil ↑ lacrimal gland secretions
Submandibular and parotid glands	viscous salivary secretions (α)	watery salivary secretions

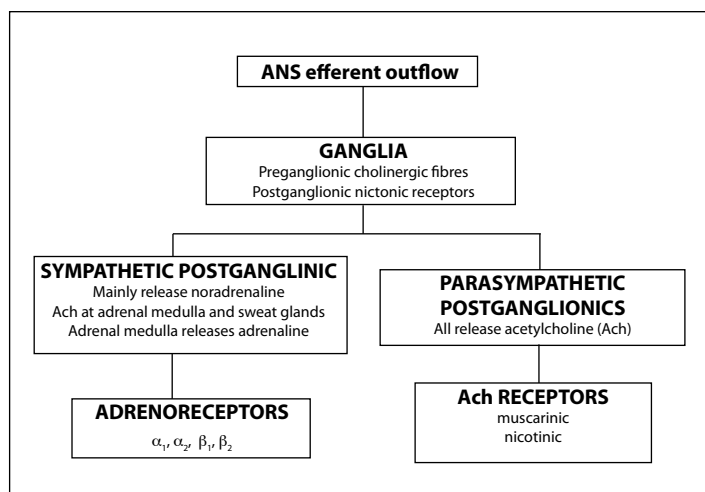


Figure 3. Summary of receptor types and neurotransmitters within the autonomic nervous system

levels. This predominantly leads to excitatory effects, such as smooth muscle contraction. α_1 -receptors are widespread in the peripheral vascular tree and stimulation causes vasoconstriction, increased systemic vascular resistance and diversion of blood flow from the peripheries to the vital organs. They can be further subdivided into α_{1a} , α_{1b} , and α_{1c} based on receptor structure and agonist response but at the moment there is no clinical difference between them.

Within the ANS, α_2 -receptors are largely presynaptic. They act via the G-protein subgroup Gi, inhibiting adenylate cyclase, reducing cytoplasmic cyclic AMP and calcium levels. They may also have a direct action – the activation of potassium channels, causing membrane hyperpolarization. The net effects of these responses are to down-regulate, or at least reduce the sympathetic response. α_2 -receptors are also present in parts of the CNS – particularly the locus coeruleus in floor of the fourth ventricle. Their function appears to be linked to the thalamus, reticulospinal tracts and vasomotor centre, with activation causing analgesia, drowsiness and hypotension. α_2 -receptors can be also subdivided into four further subtypes.

β -receptors

β -receptors are again G-protein linked receptors; stimulation leads to increased activity of adenylate cyclase that in turn increases intracellular cyclic AMP. There are three major subgroups of β -receptors – β_1 , β_2 and β_3 and recently a fourth has been described, but as yet it is not certain of its exact function. β_1 and β_4 -receptors predominate in the heart (about 85%), but the traditional view that β_1 are ‘cardiac’ and β_2 are peripheral is probably an over-simplification. The β -receptor population is rather fluid in nature – receptors can be down or up regulated in terms of number and function. A good example of this is seen in cardiac failure, where reduced receptor density is observed in cardiac muscle.

Clinically, β_1 -receptor stimulation leads to increased heart rate and positive inotropy. Renin release from the juxtaglomerular apparatus is stimulated leading to activation of the renin/angiotensin/aldosterone axis. β_2 -receptor stimulation causes relaxation of bronchial and uterine smooth muscle, vasodilatation in some vascular beds (e.g. skeletal muscle, pulmonary, coronary) and some degree of positive inotropy and chronotropy. β_3 -receptors are found in adipose tissue and have a role in regulating metabolism, thermogenesis and body fat.

ACETYLCHOLINE RECEPTORS

Acetylcholine receptors are named according to the agonist that they responded to experimentally. Those activated by nicotine are termed nicotinic receptors, whereas those that responded to muscarine are named muscarinic receptors.

Nicotinic receptors

Nicotinic receptors are ion channels that, when stimulated by acetylcholine, allow a flow of cations into the cell causing depolarization. They are found in all autonomic ganglia. Acetylcholine receptors at the motor end plate of the neuromuscular junction are historically nicotinic, but their structure differs slightly from those of the ANS.

Muscarinic receptors

Muscarinic receptors mediate the majority of effects caused by parasympathetic postganglionic fibres. Like adrenoceptors, they are G-protein linked receptors and are further divided by structure and location into subtypes M1 – M5. M1 receptors are found on gastric parietal cells and stimulate acid secretion. M2 receptors are found in the heart and have negatively chronotropic effects. M3 receptors promote smooth muscle contraction in the gut, and promote lacrimal secretion. M4 receptors cause adrenaline release from the adrenal medulla in response to sympathetic stimulation, and M5 receptors are thought to have CNS effects.

SUMMARY

The autonomic nervous system controls non voluntary bodily functions in a reflex arc with afferent signals being processed either locally or in the brain stem. Its function and dysfunction are important to anaesthetists in that many of the drugs used in anaesthesia and intensive care are used to specifically modulate autonomic receptors in the control of the cardiorespiratory and neurologic systems. Other drugs have unwanted autonomic side-effects which need to be treated (such as using an anticholinergic when reversing neuromuscular blockade). We must take into account the autonomic dysfunction seen in such widespread scenarios as diabetes, Guillan-barre syndrome and tricyclic antidepressant overdose and we must also be aware of the “normal” dysautonomia seen with old age as this can exaggerate the effects of many anaesthetic agents and techniques.

The Physiology of the Neuromuscular Junction

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THE MOTOR NEURONE

Motor neurones are the nerves that control skeletal muscle activity. They originate in the ventral horn of the spinal cord and travel up to a metre to the muscles they supply. The cell body of a neurone is at its proximal end and impulses travel from here down the axon. Axons are 10-20 micrometers in diameter and surrounded by a myelin sheath, produced by Schwann cells. This acts as insulation to speed up nerve conduction. The myelin sheath is interrupted by nodes of Ranvier between which the action potential jumps, allowing rapid conduction of the nerve impulse (saltatory conduction).

Each motor neurone connects to several skeletal muscle fibres to form a motor unit. The number of muscle fibres within the motor unit varies enormously, from a few, for fine motor control (e.g. the muscles of the eye), to several thousand for coarse actions (e.g. the thigh muscles). There is however only one neuromuscular junction on each skeletal muscle fibre, with all others being eliminated during development.

As the motor neurone enters a muscle, the axon divides into telodendria, the ends of which, the terminal buttons, synapse with the motor endplate. The two are separated by approximately 20nm, the junctional gap or synaptic cleft. It is here that release

of the neurotransmitter acetylcholine occurs with consequent binding to the receptors on the motor endplate.

THE MOTOR ENDPLATE

The motor endplate is a highly specialised region of the sarcolemma of a muscle fibre. It is oval in shape and covers an area of about 3000mcm². Its surface is deeply folded with multiple crests and secondary clefts. The nicotinic acetylcholine receptors are located on the crests of the folds in great numbers (1-10 million) and concentration (10,000-20,000 per mcm²) to ensure the success of this effector system. The clefts of the motor endplate contain acetylcholinesterase.

The area of muscle around the motor endplate is called the peri-junctional zone. Here the potential developed at the endplate is converted to an action potential that propagates through the muscle to initiate contraction. The peri-junctional zone has an enhanced ability to produce a wave of depolarisation through the muscle from that produced by the post-synaptic receptors.

ACETYLCHOLINE SYNTHESIS, STORAGE AND RELEASE

Acetylcholine is synthesised from choline and acetyl-coenzyme A (acetyl-coA) in the terminal axoplasm of motor neurones, catalysed by the enzyme choline acetyltransferase. Acetyl-coA is synthesised from pyruvate in the mitochondria in the axon terminals. Approximately 50% of the choline is extracted from extracellular fluid by a sodium dependant active transport system, the other 50% is from acetylcholine breakdown at the neuromuscular junction. Overall, the majority of the choline originates from the diet with hepatic synthesis only accounting for a small proportion.

Choline acetyltransferase is produced on the ribosomes in the cell body of the motor

Summary

The neuromuscular junction is made up of a motor neurone and a motor endplate with a synaptic cleft or junctional gap dividing them. It is critical in the production of skeletal muscle contraction.

An understanding of the structure and physiology of the neuromuscular junction is essential for the safe use of muscle relaxant drugs used in anaesthesia and intensive care, and for understanding pathological states affecting the neuromuscular junction.

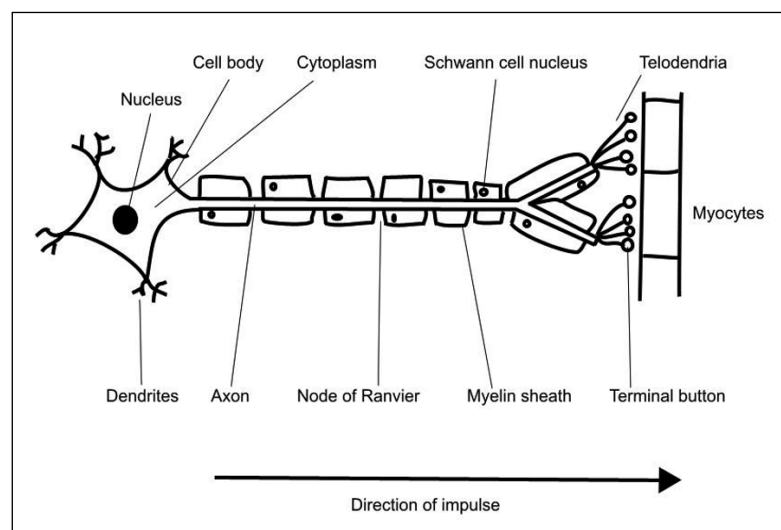


Figure 1. The motor neurone

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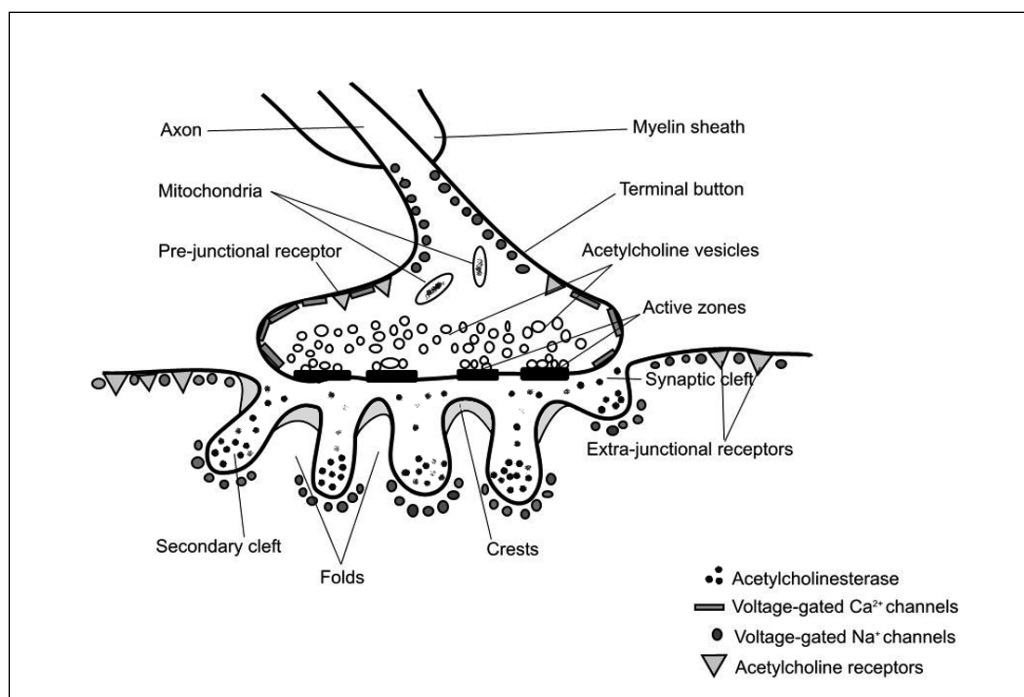


Figure 2. The neuromuscular junction

neurone from where it is transported distally by axoplasmic flow to the terminal button and can be found in high concentrations. The activity of choline acetyltransferase is inhibited by acetylcholine and increased by nerve stimulation.

Once synthesised the molecules of acetylcholine are stored in vesicles within the terminal button, each vesicle containing approximately 10,000 molecules of acetylcholine. These vesicles are loaded with acetylcholine via a magnesium dependent active transport system in exchange for a hydrogen ion. The vesicles then become part of one of three pools or stores, each varying in their availability for release. About 1% are immediately releasable, about 80% are readily releasable and the remainder form the stationary store. The exact proportions may vary depending on the level of demand or nerve stimulation.

The release of acetylcholine into the synaptic cleft may be spontaneous or in response to a nerve impulse. Spontaneous release of single vesicles of acetylcholine occurs randomly and results in miniature endplate potentials (MEPP) of 0.5-1mV, the function of which is unknown. With the arrival of a nerve impulse, large numbers of P-type calcium channels in the terminal membrane of the nerve open, allowing calcium to enter the cell. The combination of depolarisation of the presynaptic terminal and influx of calcium triggers 100-300 vesicles to fuse with the presynaptic membrane at specific release sites opposite the junctional folds and release acetylcholine into the synaptic cleft (exocytosis). This causes a brief depolarisation in the muscle that triggers a muscle action potential (see below). The depleted vesicles are rapidly replaced with vesicles from the readily releasable store and the empty vesicles are recycled. At rest the free calcium concentration is kept below 10⁻⁶M (molar) by a low membrane permeability to calcium, an active sodium/calcium exchange pump and mitochondrial sequestration.

ACETYLCHOLINE RECEPTORS

The post-junctional membrane receptors of the motor endplate are nicotinic acetylcholine receptors. There are on average 50 million acetylcholine receptors on a normal endplate, situated on the crests of the junctional folds. Each nicotinic receptor is a protein comprised of five polypeptide subunits that form a ring structure around a central, funnel-shaped pore (the ion channel). The mature adult receptor has two identical α (alpha) subunits, one β (beta), one δ (delta) and one ϵ (epsilon) subunit. In the fetus a γ (gamma) subunit replaces the ϵ . These different proteins are each coded by a different gene and synthesised within the muscle cells. The whole receptor spans the muscle cell membrane projecting predominantly extracellularly.

Acetylcholine molecules bind to specific sites on the α subunits and when both are occupied a conformational change occurs, opening the ion channel for just 1msec. The channel allows movement of all cations, however it is the movement of sodium that predominates in terms of both quantity and effect. This causes depolarisation, the cell becomes less negative compared with the extracellular surroundings. When a threshold of -50mV is achieved (from a resting potential of -80mV), voltage-gated sodium channels open, thereby increasing the rate of depolarisation and resulting in an endplate potential (EPP) of 50-100mV. This in turn triggers the muscle action potential that results in muscle contraction. By this method the receptor acts as a powerful amplifier and a switch (acetylcholine receptors are not refractory).

In addition to the post-junctional receptors on the motor endplate, acetylcholine receptors can also be found outside the neuromuscular junction and are called extra-junctional receptors, or on the pre-terminal bulb and are called pre-junctional receptors. The extra-junctional receptors can be present anywhere on the muscle membrane usually in extremely small numbers, though they are found in their greatest concentration around the endplate in the peri-junctional zone. Denervation injuries and burns are associated with large increases in the number of extra-junctional receptors on the muscle membrane. The extra-junctional receptors have the structure of immature foetal receptors (ϵ subunit replaced by a γ subunit). This affects the physiology and pharmacology of the receptor with increased sensitivity to depolarising muscle relaxants and reduced sensitivity to non-depolarising muscle relaxants.

Pre-junctional receptors on the terminal bulb have a positive feedback role. In very active neuromuscular junctions acetylcholine binds to these receptors and causes an increase in transmitter production via a second messenger system. These receptors may also play a role in the 'fade' seen in non-depolarising muscle relaxant blockade by inhibiting replenishment of acetylcholine.

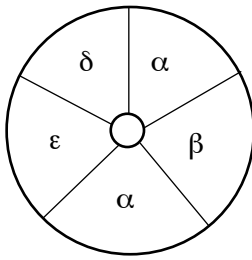


Figure 3. Cross section of the acetylcholine receptor

ACETYLCHOLINESTERASE

In order for the acetylcholine receptor to function effectively as a 'switch' it is essential that acetylcholine is removed rapidly from the junctional gap or synaptic cleft. This is achieved by hydrolysis of acetylcholine to choline and acetate in a reaction catalysed by the enzyme acetylcholinesterase (AChE). The active site in the AChE

molecule has two distinct regions, an ionic site possessing a glutamate residue and an esteratic site containing a serine residue. Hydrolysis occurs with transfer of the acetyl group to the serine group resulting in an acetylated molecule of the enzyme and free choline. The acetylated serine group then undergoes rapid, spontaneous hydrolysis to form acetate and enzyme ready to repeat the process. The speed at which this occurs can be gauged by the fact that approximately 10,000 molecules of acetylcholine can be hydrolysed per second by a single site.

This enzyme is secreted by the muscle cell but remains attached to it by thin collagen threads linking it to the basement membrane. Acetylcholinesterase is found in the junctional gap and the clefts of the post-synaptic folds and breaks down acetylcholine within 1ms of being released. Therefore the inward current through the acetylcholine receptor is transient and followed by rapid repolarisation to the resting state.

Body Fluid Compartments, Sodium and Potassium

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Summary

Disorders of sodium (Na^+) and potassium (K^+) are amongst the most common metabolic abnormalities encountered by anaesthetists. They can be caused by a wide variety of pathological processes, and if untreated, can very quickly become life-threatening. A good understanding of the basic physiology is essential to complement the principles of assessment and treatment. In this article the underlying physiology is described with frequent reference to relevant clinical situations.

FLUID AND ELECTROLYTE PHYSIOLOGY

Fluids and electrolytes are present in a number of 'compartments' in the body, according to their chemical composition. Plasma is the fluid component of blood surrounding the red cells, intracellular fluid (ICF) is the fluid within the body's cells, and interstitial fluid (ISF) is the fluid found between the cells, outside blood vessels.

Water is present in plasma, ISF and ICF and passes freely between compartments under the influence of osmotic pressure gradients. The ISF and plasma together make up the extra cellular fluid (ECF). Water accounts for 60% of adult body weight (total body water (TBW) = 42 litres for a 70kg adult). Two thirds of this is ICF (28 litres) and one third ECF (14 litres). The ECF can then be further subdivided into ISF (three quarters - 10.5 litres) and plasma (one quarter - 3.5 litres) (Figure 1).

The ECF contains most of the sodium in the body, with equal sodium concentrations in the ISF and plasma. Sodium and water can pass freely through capillary membranes whilst albumin (the most

important oncotically active constituent of the ECF) does not. Albumin is unequally distributed in the intravascular and interstitial compartments (normal concentrations of 40g.l^{-1} and 10g.l^{-1} respectively) and is excluded from the intracellular compartment. This distribution helps to retain fluid within the plasma due to the osmotic effect of albumin.

FLUID REPLACEMENT

Fluid replacement should address daily maintenance requirements and additional losses. Maintenance fluid, for patients who are unable take fluid enterally, should provide at least the minimal requirements of water, sodium and potassium. Remember that water and electrolyte requirements may increase in certain disease processes such as diarrhoea and vomiting.

TYPES OF INTRAVENOUS FLUID

Crystalloid

Crystalloids are substances which contain relatively small molecules that dissociate into ions to form true solutions, and are therefore capable of passing through

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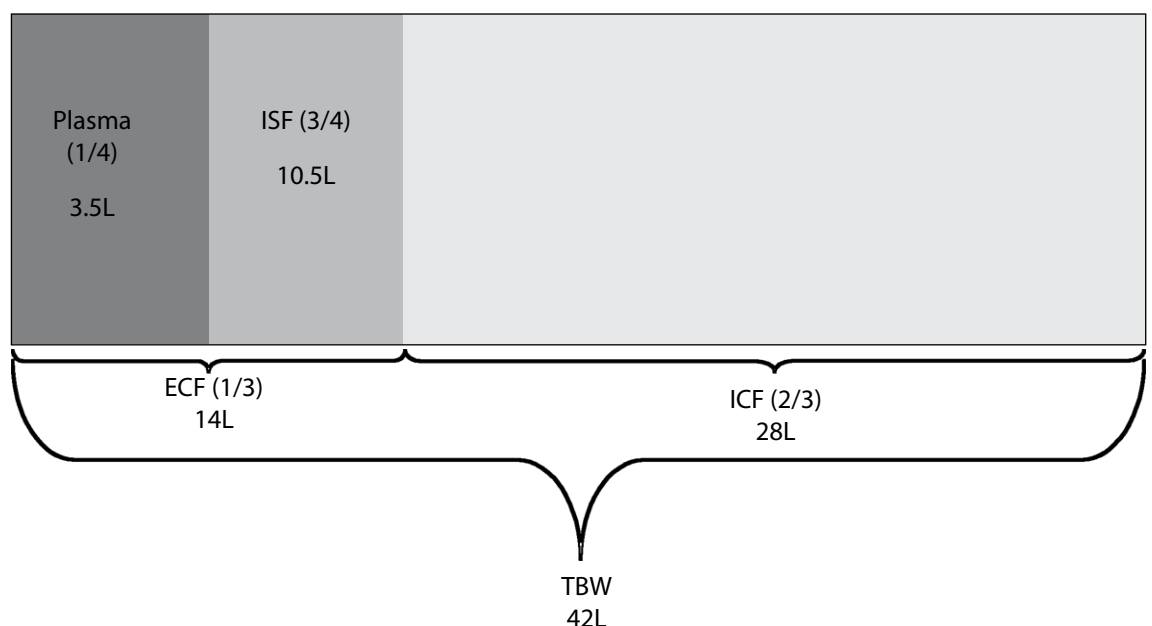


Figure 1. The theoretical fluid compartments of a 70kg individual

a semi-permeable membrane. Commonly used crystalloids include 0.9% saline, glucose and Hartmann's (Ringer's lactate) solution. The electrolyte content (mmol.l⁻¹), pH and osmolarity (mmol.l⁻¹) of these crystalloids are shown in Table 1.

On intravenous infusion, 0.9% saline and Hartman's solution rapidly distribute into the entire ECF, leaving 1/4 of the infused volume in the IVS, i.e. 250ml of a 1000ml fluid bolus.

5% glucose (the optical isomer 'dextrose' is now rarely found) loses all of its glucose on first pass through the liver and skeletal muscles. The remaining water is distributed evenly throughout the entire TBW, leaving only 1/12 of the original volume in the intravascular space (IVS) (i.e. only 83ml of a 1000ml fluid bolus).

Colloids

Colloids contain larger molecules that are dispersed throughout a solvent, i.e. they do not dissolve to form solutions. They cannot pass through semi-permeable membranes and consequently tend to remain in the IVS. The electrolyte content (mmol.l⁻¹), pH and osmolarity (mmol.l⁻¹) of some commonly used colloids are shown in Table 2.

Gelatins (e.g. GELOFUSINE, HAEMACCEL)

These colloids are polysaccharides, derived from gelatine, which are in turn derived from collagen and have an average molecular weight of 35,000 Daltons. (A Dalton or 'atomic mass unit' is a unit of mass equal to 1/12 the mass of carbon 12, which is assigned a mass of 12.) Their half-life in the IVS is approximately 3 hours and they are renally excreted. Anaphylactic reactions have been reported with an incidence of 1 in 13,000. Gelatin solutions may interfere with platelet function and coagulation via a reduction in levels of von Willebrand factor.

Dextrans (e.g. dextran 40, dextran 70)

A dextran is a polysaccharide, derived from sucrose by the action of the bacterium *Leuconostoc mesenteroides*. Dextran 40 has a molecular weight of 40,000 Daltons and dextran 70 a molecular weight of 70,000 Daltons. The intravascular half-life increases with molecule size and ranges from 15 minutes to several days. The smaller molecular weight dextrans are predominantly excreted unchanged by the kidney (accounting for up to 70% of Dextran 40), while the larger molecular weight dextrans are retained in the circulation for several days. Dextrans have an incidence of anaphylaxis of 1 in 4,500.

Dextrans are rarely used for fluid resuscitation, but they have found a role in thrombo-embolic prophylaxis via volume expansion, reduction in viscosity, and lowering platelet and erythrocyte aggregation. Side-effects include renal failure (due to tubular obstruction), interference with cross matching and coagulopathy.

Starches (e.g. hydroxyethyl starch (HES), Hetastarch)

These synthetic colloids are of similar structure to glycogen, consisting of chains of glucose molecules (>90% amylopectin). They have molecules with a large range of molecular weights, with the smaller molecules (approximately 50,000 Daltons) excreted by the kidney and the larger molecules slowly broken down by alpha-amylase hydrolysis of glycosidic bonds, yielding molecules small enough for renal clearance.

Anaphylactic reactions are rare with an incidence of 1 in 16,000. Slight prolongation of coagulation may occur after large infusions, and pruritis has also been reported. Total dose should not exceed 20ml.kg⁻¹ (1500ml.day⁻¹ for an average male).

Human Albumin Solutions

Human albumin solutions are derived from human plasma by fractionation, and then heat sterilised to reduce the risk of infective

Table 1. Comparison of the constituents of different crystalloids

	Na ⁺	K ⁺	Ca ²⁺	Cl ⁻	HCO ₃ ⁻	Osmolarity	pH
0.9% sodium chloride	154	0	0	154	0	300	5
5% glucose	0	0	0	0	0	280	4
4% glucose, 0.18% sodium chloride	30	0	0	30	0	255	4
Hartmann's	131	5	2	111	29	278	6

Table 2. Comparison of different colloids

	Na ⁺	K ⁺	Ca ²⁺	Cl ⁻	Mg ²⁺	Osmolarity	pH
Gelofusine	154	0.4	0.4	125	0.4	279	7.4
Haemaccel	145	5.1	6.25	145	0	301	7.3
Dextran 70	0	0	0	0	0	287	3.5-7.0
4.5% Human albumin solution	100-160	<2	0	100-160	0	270-300	6.4-7.4

transmission. They are presented as either 4.5% (40-50g.l⁻¹) or 20% (150-200g.l⁻¹) solutions in 0.9% saline. Traditionally albumin solutions were used as colloid in patients who were hypoalbuminaemic or where high albumin loss was anticipated (e.g. burns), and in the resuscitation of children.

DISTRIBUTION OF SODIUM AND POTASSIUM

The distribution of Na⁺ and K⁺ can be thought of as opposite - where one is found abundantly, the other is at low concentration. Sodium is the most prevalent cation in the ECF, with a normal level of around 140mmol.l⁻¹, but has a typical intracellular concentration of around 10mmol.l⁻¹. In contrast, potassium is the most prevalent cation in the ICF, with a concentration around 150mmol.l⁻¹. Because the intracellular space is the largest fluid compartment in the body, this makes it the most abundant cation overall. Only around 1% of total body K⁺ is found in the plasma, and levels are kept between 3.5 and 4.5mmol.l⁻¹.

The cell membrane acts as the barrier between the potassium-rich ICF and the sodium-rich ECF. While it allows free passage of water and non-polar, hydrophobic molecules, it is impermeable to large molecules or charged particles. Hence Na⁺ and K⁺ can only cross where specific carrier proteins allow them to do so.

In vivo, the membrane remains relatively impermeable to both Na⁺ and K⁺ most of the time. Excitable cells can change their permeability to allow the influx and efflux of ions that constitute an action potential. At rest, the large concentration gradients for Na⁺ and K⁺ are maintained by the action of Na⁺/K⁺-ATPase, a transmembrane protein which pumps out 3 Na⁺ for each 2 K⁺ it pumps in. This also maintains the net negative resting membrane potential since it involves a net transfer of one positive charge out of the cell on each cycle.

Although the Na⁺/K⁺-ATPase maintains the concentration gradients across the cell membrane, other mechanisms are in overall control of total body Na⁺ and K⁺ levels.

SODIUM HOMEOSTASIS

The volume of circulating plasma is vitally important to the body, since an adequate plasma volume is required for normal tissue perfusion. The plasma volume is proportional to the ECF volume, and since Na⁺ is the major cation of the ECF, total body Na⁺ content is proportional to ECF volume.

In normal individuals, the kidney strives to achieve Na⁺ balance - that is, to have Na⁺ excretion equal to Na⁺ ingestion. Long-term control of blood pressure is achieved by the excretion or retention of Na⁺ (and hence plasma volume) in the kidney.

The vast majority (99-99.5%) of the Na⁺ that is filtered by the kidney is reabsorbed in the proximal tubule and the loop of Henle. This reabsorption seems to be largely fixed, even in sodium overload. There is much greater control over the 0.5% of filtered Na⁺ reabsorbed in the distal tubule and collecting ducts. It is this proportionately tiny amount, that allows the body to either retain sodium and water or excrete them when necessary. Various hormones influence this balance of retention and excretion.

Hormones increasing sodium reabsorption

Renin

- Released from the juxtaglomerular apparatus of the kidney.
- Release is stimulated by:
 - raised sympathetic tone
 - falling plasma volume, and
 - certain prostaglandins, such as PGE₂.
- It has no direct effects promoting Na⁺ retention, although it controls the renin-angiotensin-aldosterone axis.

Angiotensin II

- Levels rise as result of renin release.
- In turn, it stimulates the release of aldosterone.
- Also increases tone in the efferent glomerular arteriole. This leads to an increased filtration fraction, and hence a higher oncotic and lower hydrostatic pressure in the downstream, peritubular capillary. The net effect is to enhance Na⁺ reabsorption from the proximal tubule.

Aldosterone

- Steroid hormone released from the adrenal cortex.
- End product of the renin-angiotensin-aldosterone system.
- Acts on the distal tubule and collecting duct of the kidney to increase Na⁺ and water reabsorption (proportionately more Na⁺ than water).
- Aldosterone release is also potentiated by hyperkalaemia.

Anti-diuretic hormone (ADH) also known as Arginine vasopressin (AVP)

- Posterior pituitary peptide hormone, under direct control from the hypothalamus.
- Two different receptor systems influence its release:
 - Osmoreceptors in the hypothalamus itself sense changes in plasma osmolarity. ADH levels are either increased or decreased to keep osmolarity constant. A rising serum osmolarity is also the trigger for the thirst response.
 - Baroreceptors in the carotid bodies sense changes in circulating volume - a fall in circulating volume causes a large increase in ADH concentration.
- The stress response, as triggered by surgery, also causes ADH release.
- Acts to cause passive absorption of water from the collecting ducts, concentrating the urine.
- Also causes a small degree of Na⁺ reabsorption, but the retention of water is proportionately much greater.
- Through its effects on total body water it can markedly affect the Na⁺ concentration.

- In the absence of ADH activity (diabetes insipidus) there is an inability to concentrate the urine at all, with a resultant diuresis of up to 20 litres per day.

Hormones increasing sodium excretion

Atrial natriuretic peptide (ANP)

- The main hormone opposing the above effects.
- A small peptide produced from the atrial wall as a result of atrial stretching due to hypervolaemia.
- Acts to increase Na^+ (and hence water) excretion by increasing glomerular filtration rate and blocking Na^+ reabsorption in the proximal collecting duct of the kidney.
- Some evidence suggests that other factors secreted by the hypothalamus, termed brain natriuretic peptides (BNP), may have similar roles.

POTASSIUM HOMEOSTASIS

Small increases in the serum potassium concentration can be very quickly life-threatening. The kidneys cannot excrete potassium quickly enough to contain surges due to oral potassium loads, and hence intracellular buffering plays an important role in homeostasis. As the kidneys excrete the excess and serum concentration falls, K^+ is released again from the cells.

Factors enhancing potassium transport into cells

Insulin

- via an increase in Na^+/K^+ -ATPase activity.

Adrenaline/epinephrine

- via its action on beta-adrenoceptors.

Aldosterone

- Release stimulated by rising serum potassium levels.

Serum pH

- As the pH falls, H^+ enters the cells. If the rising H^+ is due to accumulation of organic acid (e.g. lactate), the anion is able to permeate the cell along with its hydrogen ion. However, if there is accumulation of mineral acid (e.g. HCl) the inorganic ion will not cross the membrane. The cell must then excrete another cation to maintain electrical neutrality - and since K^+ is most abundant, it is often exchanged. In the opposite situation, as pH rises the cells release H^+ and in exchange take up potassium.

In the normal state 90% of daily potassium intake is excreted via the kidneys and the rest via the colon. Around 90% of the filtered potassium load is reabsorbed by the start of the distal tubule, and this figure is largely constant through a wide range of potassium intake. The overall urinary excretion of K^+ is therefore controlled by the distal tubule and collecting ducts.

In these parts of the kidney, reabsorption of Na^+ through specialised channels provides a substrate for Na^+/K^+ -ATPase on the basolateral cell surface, and hence movement of K^+ from the peritubular fluid

into the lumen. This is enhanced by a negative electrical gradient in the intraluminal fluid (since Na^+ is reabsorbed without its anion). In situations of potassium depletion, a K^+/H^+ -ATPase on the luminal membrane exchanges K^+ for hydrogen ions, helping to explain the metabolic alkalosis often encountered in potassium deficiency.

Factors influencing renal potassium handling

Aldosterone

- Enhances activity of Na^+/K^+ -ATPase in the distal tubule and collecting duct; secretion is directly stimulated by high potassium levels.

Glucocorticoids

- Act on the same renal components as aldosterone - usually metabolized by renal 11- β -hydroxysteroid dehydrogenase, but in glucocorticoid excess this enzyme can be overwhelmed, which is the cause of hypokalaemia seen in steroid treatment or Cushing's Syndrome.

Increased tubular flow rate (seen with volume expansion)

- The increased flow 'washes out' or dilutes the K^+ excreted into the tubule, favouring further K^+ excretion down a concentration gradient.

Extracellular pH

- K^+ is exchanged for H^+ in the tubular fluid.
- Alkalosis enhances H^+ reabsorption, and hence Na^+ excretion, and acidosis has the opposite effect.

Diuretics

- Enhance flow rate to the distal tubule, increasing potassium washout (as above).
- Loop diuretics (furosemide) also reduce K^+ reabsorption from the thick ascending limb of the loop of Henle.
- Potassium-sparing diuretics (amiloride, triamterene) block Na^+ reabsorption in the late distal tubule and collecting duct. Since this Na^+ influx creates the negative electrical gradient in the tubule fluid driving K^+ excretion, they lead to a decrease in potassium excretion.
- Spironolactone is an aldosterone antagonist and hence blocks Na^+ reabsorption and K^+ excretion in the collecting ducts.

CAUSES OF HYPONATRAEMIA

Consideration of the osmotic state of the patient is essential in the evaluation of hyponatraemia:

Normal osmolarity - pseudohyponatraemia

- Due to a measurement error which can result when the solid phase of plasma (that due to lipid and protein) is increased.
- Typically caused by hypertriglyceridaemia or paraproteinaemia.

High osmolarity - translocational hyponatraemia

- Occurs when an osmotically active solute that cannot cross the cell membrane is present in the plasma.

- Most solutes such as urea or ethanol can enter the cells, and cause hypertonicity without cell dehydration.
- However, in the case of the insulinopenic diabetic patient, glucose cannot enter cells and hence water is displaced across the cell membrane, dehydrating the cells and 'diluting' the sodium in the serum.
- This is also the cause of hyponatraemia seen in the TURP syndrome, in which glycine is inadvertently infused to the same effect.

Low osmolality - true hyponatraemia

True hyponatraemia is always a hypo-osmolar condition. The next stage is to consider the volume status of the patient:

Hypovolaemic hyponatraemia

- Loss of both sodium and water, but proportionately more sodium.
- Caused by solute and water losses from either a renal or gastrointestinal source.
- Usually these patients are consuming water or hypotonic fluid, although not in quantities sufficient to restore normovolaemia.
- An estimation of the urinary sodium level can be helpful: a level below 30mmol.l⁻¹ suggests an extrarenal cause, while a level above 30mmol.l⁻¹ suggests a primary renal problem.

Euvolaemic hyponatraemia

- The most common form seen in hospitalized patients.
- May have a slight increase or decrease in volume, but it is not clinically evident, and they do not have oedema.
- The most common cause is the inappropriate administration of hypotonic fluid.
- The syndrome of inappropriate ADH secretion (SIADH) also causes euvolaemic hyponatraemia; in order to make this diagnosis one must first exclude renal, pituitary, adrenal or thyroid dysfunction, and the patient must not be taking diuretics.

Hypervolaemic hyponatraemia

- Characterised by both sodium and water retention, with proportionately more water.
- Therefore have an increased amount of total body sodium.
- Causes are all characterised by disordered water excretion, and are usually easy to diagnose.

CAUSES OF HYPERNATRAEMIA

Hypernatraemia is either caused by excessive salt intake, or (much more frequently) inadequate water intake. As with hyponatraemia, consideration of the volume status of the patient is essential.

Hypovolaemic hypernatraemia

- Loss of both sodium and water, but relatively more water.
- An estimation of the urinary sodium level can be helpful: a level below 30mmol.l⁻¹ suggests an extrarenal cause, while a level above 30mmol.l⁻¹ suggests a primary renal problem.
- These patients are either not able to take in adequate fluid to replace their losses, or are prevented from doing so.

Euvolaemic hypernatraemia

- Occurs when body water losses are partially replaced.
- May be due to a lack of available water, or due to a blunting of the normal thirst response seen in the extremes of age.

Hypervolaemic hypernatraemia

- Seen where sodium retention is not matched by increased fluid intake.
- More uncommon than the other two types of hypernatraemia.

CAUSES OF HYPOKALAEMIA

Hypokalaemia is caused by a shift of potassium into cells, or more commonly by a total body potassium deficit. Occasionally the two situations may co-exist.

Intracellular potassium shifting

- Excess insulin (exogenous or endogenous).

Table 3. Causes of hyponatraemia

Hypovolaemic (renal)	Hypovolaemic (extrarenal)	Euvolaemic	Hypervolaemic
Diuretic excess	Vomiting	Glucocorticoid deficiency	Acute or chronic renal failure
Mineralocorticoid deficiency	Diarrhoea	Hypothyroidism	Congestive cardiac failure
Salt-wasting nephropathy	Burns	SIADH	Nephrotic syndrome
Proximal renal tubular acidosis	Pancreatitis	Many drugs (most acting via ADH pathway)	Cirrhosis
Ketonuria	Trauma	Psychogenic polydipsia	
Osmotic diuresis		Hypotonic fluid replacement	

Table 4. Causes of hypernatraemia

Hypovolaemic (renal)	Hypovolaemic (extrarenal)	Euvoalaemic	Hypervolaemic
Loop or osmotic diuretics	Diarrhoea/vomiting	Diabetes insipidus (cranial and nephrogenic)	Na ⁺ ingestion
Post obstruction of the postrenal tract	Burns	Insensible losses	Conn's syndrome
Intrinsic renal disease	Fistulae		Cushing's syndrome
			Administration of hypertonic saline, Na ⁺ HCO ₃ ⁻
			Dialysis against hypertonic dialysate

- β -adrenoceptor agonists (such as endogenous catecholamines or exogenous salbutamol).
- Theophylline toxicity.
- Acute rise in plasma pH.

Total body potassium deficit

- May result from either decreased intake or increased losses.
- Diet must be severely deficient in K⁺ over a long period in order to reach a position of clinical hypokalaemia; hence seen most commonly in alcoholics.
- Excessive losses may be either renal or extrarenal.

Renal causes include:

- Diuretics.
- Mineralocorticoid excess.
- Glucocorticoid excess.
- Renal tubular acidosis Type I and II.
- Diabetic ketoacidosis – glucose causes an osmotic diuresis, washing out potassium.
- Vomiting – this is not caused by a loss of K⁺ in the vomit, rather, loss of H⁺ and water lead to metabolic alkalosis and increased aldosterone.
- Ureterosigmoidostomy.
- Rare inherited conditions such as Bartter's and Gitelman's Syndromes.

Extrarenal causes include:

- Inadequate intake.
- Excessive perspiration.
- Chronic diarrhoea.
- Gastrointestinal fistulae.

CAUSES OF HYPERKALAEMIA

Hyperkalaemia may be due to either an overall increase in total body potassium, or an acute shift of potassium from the intracellular to the extracellular compartment.

Extracellular potassium shifts

- Acidosis – H⁺ is taken into the cell in exchange for K⁺.
- Insulin deficiency, with hyperglycaemia – note that this is often found coexistent with a profound total body potassium deficit.
- Digitalis toxicity – due to inhibition of the Na⁺/K⁺-ATPase.
- β -blockers – typically cause only a mild elevation in K⁺.
- Exercise – potassium efflux from skeletal muscle as a result of muscular contraction
- Suxamethonium administration. Fasciculations lead to an efflux of potassium from skeletal muscle, similar to the effect of exercise but more pronounced and more acute. A single 100mg dose may cause the serum potassium to rise by up to 1.0mmol.l⁻¹. If the patient already has elevated serum potassium, this may be enough to cause a fatal arrhythmia. In patients with denervated muscle, the usual mechanisms keeping the acetylcholine receptors in the synaptic cleft are disturbed, and they spread out to cover the whole of the muscle fibre (extrajunctional receptors). Suxamethonium administration is contraindicated in these patients as it causes a much bigger potassium efflux and often leads to dangerous hyperkalaemia.

Excessive potassium input

- Cellular lysis, as seen in haemolysis, rhabdomyolysis or tumour lysis syndrome.
- Inappropriate prescription of K⁺-containing IV fluids or supplements is a very important cause in hospitalized patients.

Impaired renal excretion

- Decreased GFR – renal failure is the commonest cause of hyperkalaemia.
- Mineralocorticoid insufficiency – this may be due to primary adrenal failure, hyporeninaemic hypoaldosteronism (Renal tubular acidosis type IV), or due to drugs like ACE inhibitors, Angiotensin-II receptor antagonists or spironolactone.
- Potassium sparing diuretics – see above.

- Primary renal insults (such as interstitial nephritis) causing decreased potassium excretion in the distal tubules and collecting ducts.

Pseudohyperkalaemia

- A common cause of spuriously elevated potassium levels.
- The most common causes are in vitro haemolysis, or leaving the tourniquet on for an extended period prior to blood sampling.
- It is also seen in patients with highly elevated white cell or platelet counts, due to secretion of potassium from these cells prior to laboratory analysis.

IMPLICATIONS FOR CLINICAL ANAESTHESIA

In general, the implications of an increase or decrease in the serum levels of Na^+ or K^+ are dependent on the speed with which this change occurred. Very low levels of Na^+ can be reached without appreciable symptoms if they have come about gradually over several months. Similarly, patients with chronic renal impairment can often tolerate levels of hyperkalaemia that would be fatal if they happened over a few hours. However, there seem to be limits above or below which the normal physiological processes are affected no matter how long the system takes to get there.

Patients can also be at risk from overly rapid correction of electrolyte imbalance. In deciding when and how to treat a patient, a balance must be struck between the risks of the condition, and the risks of treatment.

Effects and treatment of hyponatraemia

The normal range of serum sodium is usually quoted as being approx. 135-145mmol.l⁻¹; however, levels between 125mmol.l⁻¹ and 150mmol.l⁻¹ are often asymptomatic. Outside this range there is an increasing frequency of nausea, lethargy, weakness and confusion, and levels above 160mmol.l⁻¹ or below 110mmol.l⁻¹ are strongly associated with seizures, coma and death.

As serum sodium and osmolarity fall, water tends to enter the cells causing them to swell.

Clinically this is most important in the brain.

Several factors put patients at increased risk of complications of hyponatraemia or its treatment:

- Post-operative patients, premenopausal women, elderly women taking thiazides, children, and patients who are hypoxaemic are all at increased risk of acute hyponatraemic cerebral oedema.
- Malnourished patients, alcoholics, those with burns or hypokalaemia are all at increased risk of osmotic myelinolysis due to overly rapid correction of hyponatraemia.

A recent review of the literature has pointed out that there is as yet no consensus on the optimum treatment of dysnatraemia. However, all authorities stress the importance of distinguishing between hyponatraemia that has developed acutely (usually taken to mean over less than 48 hours) and chronic hyponatraemia. This is because of important differences in the management between the two groups.

Most authors suggest that hyponatraemia that has developed acutely (for instance, in the immediate post-operative period) can be safely treated with rapid correction. Rapid correction should only be undertaken in patients who are symptomatic, and the aim of treatment is to correct the level until the symptoms resolve. Some sources have suggested that correction by up to 2mmol.l⁻¹.h⁻¹ is safe in the initial treatment of acute hyponatraemic states. Correction to a serum Na^+ of >135mmol.l⁻¹ may be safe in this situation, but it is not necessary to correct rapidly once the symptoms have resolved.

Methods of rapid correction might include the administration of furosemide and/or hypertonic saline; however management should be by a specialist in an appropriate setting, with monitoring of serum Na^+ levels hourly.

The treatment of chronic hyponatraemia is also determined by the presence or absence of symptoms. In the presence of symptoms, a rapid correction of up to 10mmol.l⁻¹ may be permissible. Following this, however, the rate of reversal should be limited to 1.5mmol.l⁻¹.h⁻¹ and to no more than 8mmol.l⁻¹ over 24hrs. Some sources suggest that a rate of 12mmol.l⁻¹ in 24hrs is safe.

Fluid restriction is the mainstay of treatment in these patients, who need to have regular neurological assessment and rechecking of serum electrolytes at least every 12 hours. In the long-term, treatment is aimed at identifying and dealing with the underlying cause. Future advances in the shape of selective ADH (AVP) antagonists (so-called aquaretics) look set to improve the long-term management of chronic hyponatraemia.

In all cases, hypovolaemia if present must be corrected first with 0.9% saline. This removes the ADH response that is accentuating the sodium/water imbalance. In patients who are hypervolaemic, the treatment is aimed at fluid restriction, salt restriction and loop diuretics. Aquaretics may also be useful drugs for these patients as well.

While evidence is lacking that chronic hyponatraemia is associated with worse surgical outcomes, anything more than mild, asymptomatic hyponatraemia should be regarded as a relative contraindication to elective surgery.

Treatment of hypernatraemia

Firstly any volume deficit should be corrected with 0.9% saline until the hypovolaemia, as measured by orthostatic hypotension, improves. The cause of fluid loss should also be investigated and treated.

The total body water deficit can be calculated based on the serum sodium and the assumption that 60% of the body is water – this deficit should then be corrected with 5% dextrose, with half given in the first 12-24 hours, and the rest over the next 24-36 hours. In the case of hypervolaemic hypernatraemia, the removal of excess sodium is the aim, and loop diuretics or dialysis may achieve this if the patient has renal dysfunction.

Effects of hypokalaemia

The effects of hypokalaemia depend upon the serum level. A normal value of 3.5-4.5mmol.l⁻¹ is generally accepted, but levels of 3.0-3.5mmol.l⁻¹ are usually asymptomatic. Below 3.0mmol.l⁻¹ general

symptoms of weakness, lassitude and constipation are common. Below 2.5mmol.l⁻¹ muscle necrosis has been described (probably due to an inability to increase blood flow during exercise), and below 2.0mmol.l⁻¹ an ascending paralysis may be seen, eventually leading to respiratory compromise.

Patients without underlying cardiac disease are unlikely to suffer myocardial effects, even at levels below 3.0mmol.l⁻¹. However, those with ischaemic heart disease, heart failure or left ventricular dysfunction are at risk of arrhythmias with only mild or moderate hypokalaemia. Initially U-waves are seen on the ECG, with gradual sagging of the ST segment and flattening of the T-wave. Slight widening of the QRS complex and PR elongation may be seen, and there is a predisposition to both ventricular and supraventricular ectopic rhythms, especially in a patient taking digoxin.

Renal effects of hypokalaemia include metabolic acidosis, increased ammoniogenesis and numerous structural changes in the kidney if the condition persists.

As with sodium, the rapidity of the change in K⁺ level has a large influence on the severity of the symptoms.

Treatment of hypokalaemia

Once intracellular K⁺ shifts have been excluded (theophylline toxicity, hyperinsulinaemia) the treatment of hypokalaemia is aimed at replacement of potassium. Ideally, this should be oral supplementation, but if severe the initial replacement is best given intravenously, through a central vein within a critical care facility. Careless administration of intravenous potassium is the commonest cause of hyperkalaemia in hospitalized patients, so appropriate consideration should be given to this decision. In any case, the rate of administration should not exceed 20mmol.h⁻¹, and the patient should have continuous cardiac monitoring.

In the absence of factors causing potassium shifting into cells, the serum potassium is a good guide to the total body potassium deficit. A fall from 3.5 to 3.0mmol.l⁻¹ suggests a deficit in the order of 5% (around 175mmol); a decline from 3.0 to 2.0mmol.l⁻¹ suggests a further 200-400mmol deficit. Magnesium deficiency is very commonly associated with hypokalaemia and levels should be checked and magnesium replaced if appropriate.

Prophylactic administration of potassium to post-operative patients at risk of cardiac abnormalities is common practice. There is evidence that minor elevation of K⁺ (within the normal range) can reduce the incidence of electrocardiac abnormalities such as U- waves, bifid T-waves and signs of digitalis toxicity. There is some evidence to support the maintenance of K⁺ levels between 4.0-4.5 mmol.l⁻¹ in patients post cardiac surgery, and in patients on drugs such as quinidine and sotalol (which potentially predispose to Torsades de Pointes). Additionally, potassium supplementation may benefit patients with abnormal repolarisation in the context of congestive cardiac failure. However, the practice of artificially augmenting the potassium level to abolish single ventricular ectopic beats or as a routine treatment for all post-operative patients is no longer considered best practice.

Effects of hyperkalaemia

The most important effects of hyperkalaemia are on the heart. Levels

below 6.0mmol.l⁻¹ rarely cause any clinical symptoms. As the serum K⁺ level increases, ECG changes are noted: firstly peaking of the T-waves, then broadening of the P-waves and QRS-complex when the level is >7.0mmol.l⁻¹. Finally the ECG takes on a sinusoidal pattern, which is a precursor to cardiac arrest. Terminal ECG changes may develop very quickly, and even with mildly elevated potassium levels any sign of ECG involvement should prompt immediate treatment.

As with other electrolyte disturbances, the speed of onset of hyperkalaemia is very important. A relatively small increase, if it occurs over a short time, can precipitate a fatal arrhythmia where a much higher level may be tolerated (for instance, in the insidious onset of renal failure) if it has developed over a longer period.

Other sequelae of hyperkalaemia include paraesthesiae, weakness, paralysis, a decreased renal production of ammonia, an increased renal retention of H⁺ and a subsequent metabolic acidosis, natriuresis, and elevated levels of aldosterone and insulin.

Treatment of hyperkalaemia

The various therapies commonly used to reduce the K⁺ level acutely may be divided into two groups: those that seek to transiently move the potassium to the intracellular compartment, and those that seek to remove an overall surplus of potassium from the body. While the former group may be used in the vast majority of hyperkalaemic patients, not all hyperkalaemic patients have excess total body potassium.

The classic example is an acidotic patient with diabetic ketoacidosis, who has an elevated serum potassium due to cellular impermeability in the absence of insulin, but who is often profoundly depleted in potassium levels overall. Such patients require emergency management to lower the high potassium levels they present with, but as treatment commences and their cells rapidly become permeable to potassium, caution must be taken to avoid them developing a rebound hypokalaemia.

A recent Cochrane review of the efficacy of various potassium lowering therapies showed that, despite this being an exceedingly common problem in hospitalized patients, very little evidence exists to guide the practitioner towards the most effective. The therapies most often suggested for acute potassium lowering are infusions of glucose and insulin, β_2 -adrenoceptor agonists, either nebulised or inhaled, and IV sodium bicarbonate. Of these, glucose-insulin and beta-agonists both seem to be effective, and a combination seems more effective than either being used in isolation. The evidence for sodium bicarbonate is equivocal.

The same review investigated two methods for removing excess potassium from the system: K⁺-absorbing styramine resins, and dialysis. Of these, the evidence was that resins were not effective at 4hrs post administration, but longer-term studies have not been done. Dialysis was effective at decreasing total body potassium over the same period.

In addition, the administration of calcium (as either calcium gluconate or calcium chloride) is recommended as a means of rapidly reversing the repolarisation abnormalities seen in severe hyperkalaemia. Its use is supported by experimental and animal studies, but there are neither randomised trials nor any good evidence

to recommend one formulation over another. Furthermore, it must always be remembered that a cornerstone of treatment is to diagnose the underlying cause of hyperkalaemia and take steps to reverse this.

CONCLUSION

Disorders of Na⁺ and K⁺ homeostasis are very common problems, encountered in clinical practice on an almost daily basis. They are frequently mismanaged due to poor understanding of Na⁺ and K⁺ metabolism. Careless prescription of perioperative fluids and infrequent checking of electrolyte levels puts patients needlessly at risk. Often it is the most junior doctors involved in a patient's care who have responsibility for these areas.

Surgical patients are frequently affected by electrolyte imbalance.

They are often sedated or not allowed to eat and drink, and hence have intravenous fluid infusions prescribed for extended periods. Pre-operative bowel obstruction or bowel preparation can leave them profoundly dehydrated. They are subject to large fluid shifts in theatre, and post-operatively are usually in a water-retaining state due to a stress response and ADH secretion.

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Originally published in *Update in Anaesthesia*, edition 12 (2000)

Endocrine Physiology

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Key to terms used

ADH	Antidiuretic Hormone	T3	Tri-iodothyronine
GH	Growth Hormone	T4	Thyroxine
GHRH	GH Releasing Hormone	GHRH	GH Release Inhibiting Hormone
LH	Luteinising Hormone	FSH	Follicular Stimulating Hormone
TSH	Thyroid Stimulating Hormone	DDAVP	Desmopressin
ACTH	Adrenocorticotrophic Hormone	CRH	Corticotrophin Releasing Hormone

INTRODUCTION

The endocrine system acts through chemical messengers, hormones, to coordinate many bodily functions. It maintains the internal environment (homeostasis), controls the storage and utilisation of energy substrates, regulates growth and reproduction and, perhaps of greatest importance to anaesthetists, controls the body's responses to external stimuli, particularly stress.

THE PITUITARY GLAND

Anatomy

The pituitary gland lies within a dural covering in a depression of the skull base (sella turcica). On each side lie the cavernous sinus containing the carotid arteries and the III, IV and VI cranial nerves. The pituitary gland is attached to the hypothalamus in the floor of the third ventricle by the pituitary stalk (infundibulum), which passes through an aperture in the fold of dura mater forming the roof of the sella turcica (diaphragma sellae).

The pituitary gland is made up of two parts:

The posterior lobe (neurohypophysis) is the expanded inferior end of the infundibulum, and is developed embryologically from the brain. The infundibulum contains axons of neurones from the supraoptic and paraventricular nuclei of the hypothalamus which terminate on the surface of capillaries in the posterior lobe onto which they secrete the two posterior pituitary hormones, antidiuretic hormone (ADH) and oxytocin.

The anterior lobe (adenohypophysis) is much larger than the posterior lobe, and itself consists of three

parts which partly surround the posterior lobe and the infundibulum (Figure 1). The distal part forms most of the anterior lobe. The intermediate part, a thin sheet of non-functional glandular tissue and a narrow cleft separates the anterior lobe from the posterior lobe. The infundibular part of the anterior lobe is a narrow upward projection which partially encircles the infundibulum.

The blood supply to the pituitary gland is by branches of the internal carotid and anterior cerebral arteries. The anterior lobe also receives venous blood from the hypothalamus via the hypothalamo-hypophyseal portal system of veins (Figure 2), which transmits releasing factors to the pituitary from the lower tip of the hypothalamus. The veins of the pituitary drain into the cavernous sinuses.

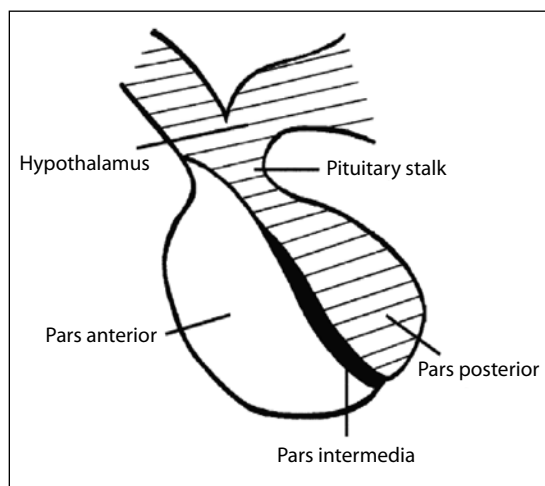


Figure 1. The pituitary gland

Summary

This article will concentrate on basic physiology of the principal endocrine glands, the pituitary, thyroid, and adrenal glands. Other endocrine glands which will not be discussed here include the pancreas, the hypothalamus, parathyroids and gonads. In addition, the liver, kidney, lungs, gastrointestinal tract, pineal gland and thymus produce many other hormone-like substances.

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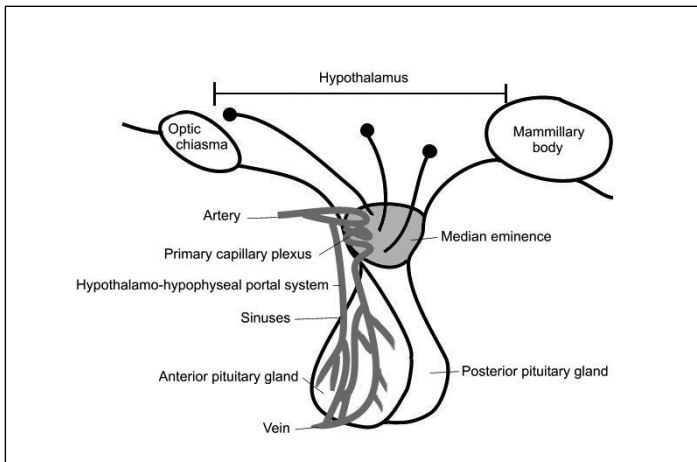


Figure 2. The hypothalamo-hypophyseal portal system

Human anterior pituitary cells have traditionally been classified according to their staining characteristics into chromophobes, acidophils or basophils. With more modern techniques of immunochemistry and electron microscopy, it is now possible to distinguish five cell types: 1. somatotropes, which secrete growth hormone (GH); 2. lactotropes, which secrete prolactin; 3. thyrotropes, which secrete thyroid stimulating hormone (TSH); 4. gonadotropes, which secrete luteinising hormone (LH) and follicle-stimulating hormone (FSH); and 5. corticotropes, which secrete adrenocorticotrophic hormone (ACTH). They control a wide range of functions (Figure 3). There are also functionally inert cells within the gland known as null cells.

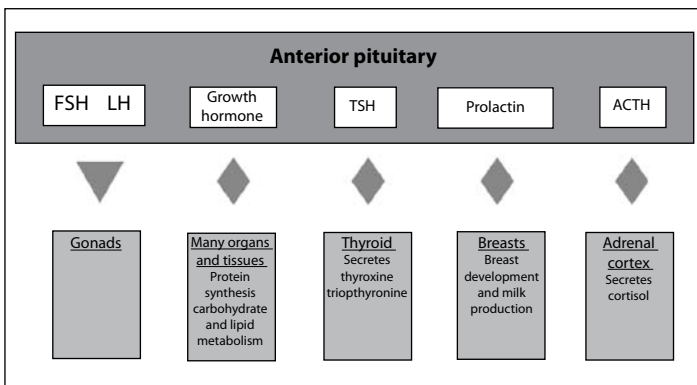


Figure 3. The widespread effects of the pituitary gland

Control of pituitary secretion by the hypothalamus

Almost all hormone secretion by the pituitary is controlled by either hormonal or nervous signals from the hypothalamus. The hypothalamus receives signals from almost all possible sources in the nervous system, and is itself under negative feedback control (Figure 4) from the hormones regulated by the pituitary gland. This means that when there is a low level of hormone in the blood supplying the hypothalamus, it produces the appropriate releasing hormone or factor which stimulates the release of the hormone by the pituitary and this in turn stimulates the target gland to produce and release its hormone. As a result, the blood level of that hormone rises and inhibits the secretion of releasing hormone or factor by the hypothalamus.

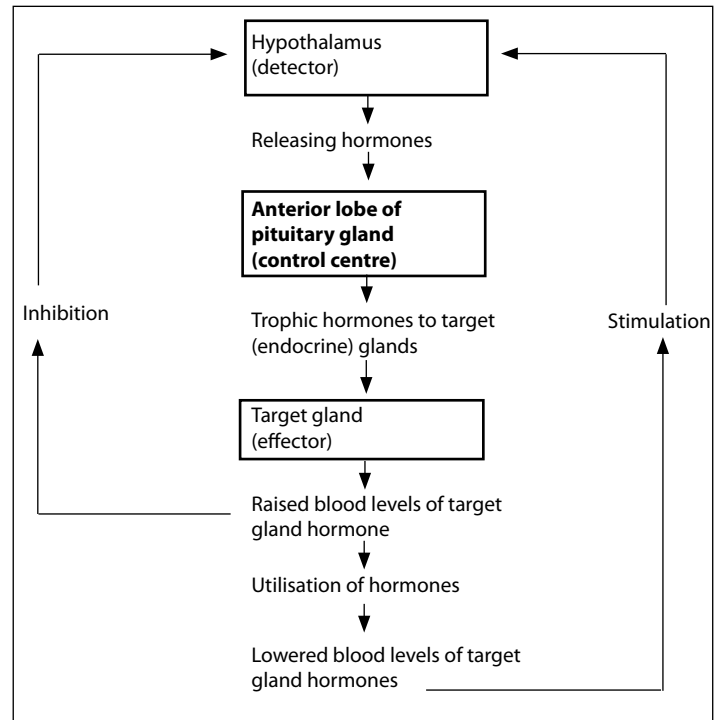


Figure 4. Negative feedback regulation of secretion of hormones by the anterior lobe of the pituitary gland

Secretion from the posterior pituitary is controlled by nerve fibres arising in the hypothalamus which pass along nerve axons and terminate on blood vessels in that part of the gland.

Secretion from the anterior pituitary is controlled by hormones called hypothalamic releasing and hypothalamic inhibitory hormones (or factors) carried from the hypothalamus to that part of the gland by the hypothalamo-hypophyseal portal system. These hormones act on the glandular cells of the anterior pituitary to regulate their secretion.

HORMONES OF THE ANTERIOR PITUITARY GLAND

Growth hormone

Effects

- Promotes the growth of bone, cartilage and soft tissue via the effects of insulin-like growth factor, IGF-1 (formerly known as somatomedin C), whose production is increased in the liver, kidney and other tissues in response to GH. If excess GH levels are present before fusion of the epiphyses occurs, gigantism occurs. After the epiphyses are closed, linear bone growth is no longer possible and excess GH leads to acromegaly, which can cause a number of clinical problems relevant to anaesthesia (Table 1).
- Increases the rate of protein synthesis in all cells of the body.
- Fat mobilisation by release of fatty acids from adipose tissue.
- Decreases the rate of glucose utilisation throughout the body due to diminished uptake of glucose by cells (i.e. it is counter regulatory to insulin).
- Increases hepatic glucose output.
- Stimulates erythropoiesis.

- Na⁺ and K⁺ excretion are reduced, while Ca²⁺ absorption from the intestine is increased.

Regulation

GH release from the anterior pituitary is under the control of the hypothalamus which secretes both a releasing hormone (growth hormone releasing hormone - GHRH) and an inhibitory hormone (growth hormone release-inhibiting hormone - GHRIH, or somatostatin) into the hypothalamo-hypophyseal portal system. GH and IGF-1 produce negative feedback effects on the hypothalamus and pituitary.

The stimuli that increase GH secretion fall into three general categories:

- Hypoglycaemia and fasting.
- Increased amounts of certain amino acids in the plasma.
- Stressful stimuli.

Secretion of GH is reduced in response to increased concentrations of glucose, free fatty acids or cortisol in the plasma, and is also reduced during rapid eye movement sleep.

Prolactin

Effects

Prolactin stimulates secretion of milk and has a direct effect on the breast immediately after parturition. Together with oestrogen and progesterone, prolactin initiates and maintains lactation.

Regulation

Secretion is tonically inhibited by the release of dopamine from the hypothalamus into the hypothalamohypophyseal portal system. Prolactin secretion can be intermittently increased by release of prolactin releasing hormone from the hypothalamus, such as when the baby suckles the breast.

Thyroid stimulating hormone

Effects

TSH increases all the known activities of the thyroid glandular cells, with increased production and secretion of thyroxine (T₄) and

triiodothyronine (T₃) by the thyroid gland. Persistently elevated levels of TSH lead to hypertrophy of the thyroid, with increased vascularity.

Regulation

TSH is produced and released from the anterior pituitary in response to thyrotropin releasing hormone released from the hypothalamus and carried to the pituitary via the hypothalamohypophyseal portal system. The hypothalamus can also inhibit TSH secretion via the effects of released somatostatin, in the same way that GH inhibition occurs. Free T₃ and free T₄ in the plasma exert a negative feedback effect on the hypothalamus and the pituitary to regulate the circulating levels of these hormones.

Follicle stimulating hormone and luteinizing hormone

Effects

In men, FSH stimulates spermatogenesis by the Sertoli cells in the testis. In females, FSH causes early maturation of ovarian follicles. In men, LH causes testosterone secretion by the Leydig cells in the testis. In females, LH is responsible for the final maturation of ovarian follicles and oestrogen secretion from them.

Regulation

In males and females, LH and FSH production by the anterior pituitary is regulated by release of gonadotropin releasing hormone from the hypothalamus, which is carried to the pituitary in the hypothalamohypophyseal portal system. Feedback effects of testosterone, oestrogen and inhibin (produced in the testes and ovaries in response to FSH stimulation) on the hypothalamus and anterior pituitary regulate the levels of circulating LH and FSH.

Adrenocorticotrophic hormone (ACTH)

ACTH is formed in the anterior pituitary by enzymatic cleavage of the prohormone pro-opiomelanocortin (POMC). This polypeptide is hydrolysed in the corticotropes to produce ACTH and β-lipotrophin (β-LPH). Some of the β-LPH is split to produce β-endorphin. The anterior pituitary secretes all three hormones - ACTH, β-LPH and β-endorphin. The physiologic role of β-LPH is unknown, β-endorphin is an endogenous opioid peptide.

Table 1. Outline of anaesthetic problems associated with pituitary surgery for acromegaly

Problem	Management
Overgrowth of the mandible, pharyngeal and laryngeal structures May lead to difficult airway maintenance and intubation, and sleep apnoea with its complications	Careful preoperative assessment. Consider fiberoptic intubation or tracheostomy under local anaesthesia in severe cases
Cardiomyopathy with cardiac enlargement leading to congestive cardiac failure	Cardiovascular assessment including ECG and chest X-ray. Medical management of hypertension prior to surgery.
Impaired glucose tolerance	May require perioperative insulin therapy Regular assessment of blood glucose

Effects

ACTH stimulates the production of cortisol (hydrocortisone) and androgens from the zona fasciculata and zona reticularis of the adrenal cortex. ACTH also acts on the cells in the zona glomerulosa to enable them to produce aldosterone in response to increased potassium ion concentration, elevated angiotensin levels or reduced total body sodium.

Regulation

ACTH is secreted from the anterior pituitary in response to the production of corticotropin releasing hormone (CRH) from the hypothalamus, which is carried to the pituitary along the hypothalamohypophyseal portal system (Figure 5). Excitation of the hypothalamus by any type of stress causes release of CRH, leading to secretion of ACTH from the anterior pituitary and subsequent release of cortisol from the adrenal cortex. There is direct feedback of the cortisol on the hypothalamus and anterior pituitary gland to stabilise the concentration of cortisol in the plasma.

HORMONES OF THE POSTERIOR PITUITARY GLAND

Antidiuretic hormone (ADH) is formed primarily in the supraoptic nuclei of the hypothalamus, while oxytocin is formed primarily in the paraventricular nuclei. Both hormones are transported from the hypothalamus to the posterior pituitary along axons in the infundibulum. Under resting conditions, large quantities of both hormones accumulate in the endings of the nerve fibres in the posterior pituitary. Excitatory nerve impulses in these fibres from their relevant nuclei cause release of the hormones with their subsequent absorption into adjacent capillaries.

Antidiuretic hormone

Effects

ADH promotes water retention by the kidneys by causing increased permeability of the collecting ducts to water, and its subsequent reabsorption from the tubular fluid.

Regulation

ADH is secreted in response to increased plasma osmolality, decreased extracellular fluid volume, pain and other stressed states, and in response to certain drugs including morphine and barbiturates. ADH secretion is inhibited by alcohol.

Oxytocin

Effects

- Contraction of the pregnant uterus.
- Contraction of the myoepithelial cells in the lactating breast, causing ejection of milk out of the alveoli into the milk ducts and thence out of the nipple.

Regulation

Oxytocin secretion is increased during labour. Descent of the fetus down the birth canal initiates impulses in the afferent nerves that are relayed to the hypothalamus, causing release of oxytocin, which enhances labour. During suckling, touch receptors in the nipple

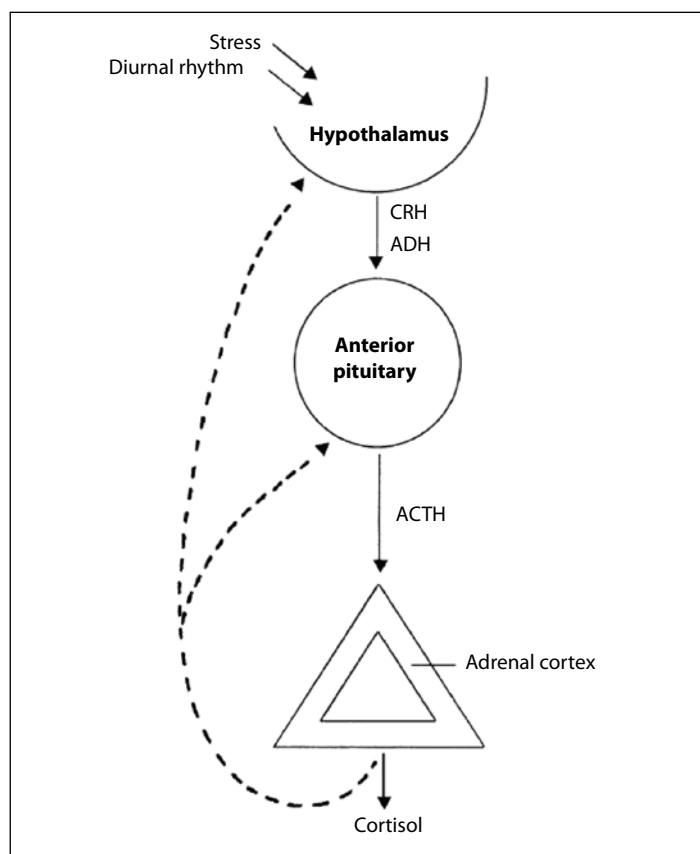


Figure 5. Control of glucocorticoid function

of the breast transmit signals that terminate in the hypothalamus resulting in release of oxytocin to eject milk.

THE THYROID GLAND

Embryology

The thyroid develops from the floor of the pharynx between the first and second pharyngeal pouches. It grows caudally as a tubular duct which eventually divides to form the isthmus and lobes. The thyroglossal duct extends from the foramen caecum, in the floor of the mouth, to the hyoid bone. The pyramidal lobe of the thyroid develops from the distal part of the duct. Aberrant thyroid tissue, for example a lingual thyroid, may develop from persistent remnants of the thyroglossal duct.

Anatomy

Although the term thyroid is derived from the Greek word meaning shield, the gland is most commonly described as ‘butterfly’ shaped. The thyroid gland lies in the neck related to the anterior and lateral parts of the larynx and trachea. Anteriorly, its surface is convex; posteriorly, it is concave. It is composed of two lobes joined by an isthmus (Figure 6). The isthmus lies across the trachea anteriorly just below the level of the cricoid cartilage. The lateral lobes extend along either side of the larynx as roughly conical projections reaching the level of the middle of the thyroid cartilage. Their upper extremities are known as the upper poles of the gland. Similarly, the lower extremities of the lateral lobes are known as the lower poles. The gland is brownish-red due to a rich blood supply.

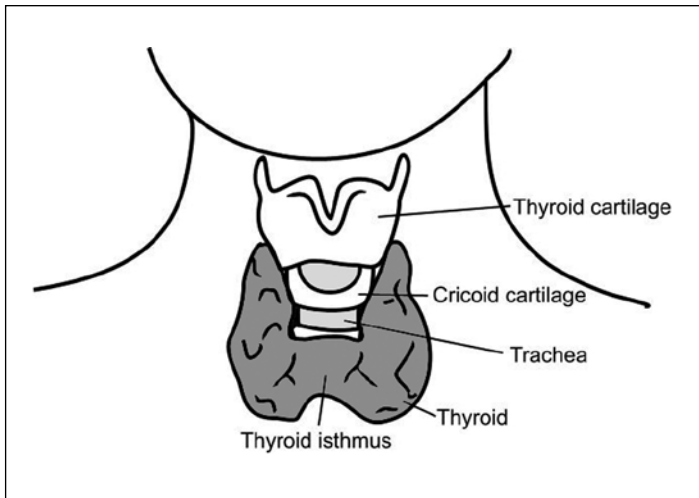


Figure 6. The thyroid gland

Histology

Each lobe is composed of spherical follicles surrounded by capillaries. The follicles comprise a single layer of epithelial cells forming a cavity that contains colloid where the thyroid hormones are stored as thyroglobulin. C-cells, which secrete calcitonin, are found outside the follicles.

Synthesis and transport of thyroid hormones

Dietary iodide is concentrated by the thyroid gland and is oxidised, in the follicle cells, to iodine. The iodine is linked to tyrosine molecules in thyroglobulin, a large protein synthesised by the follicular cells into the cavity (Figure 7). Iodinated tyrosine is coupled to form triiodothyronine (T₃) and thyroxine (T₄) which are then released into the circulation. Anti-thyroid drugs block the synthesis of T₃ and T₄ by interfering with various steps of this process, for example, carbimazole blocks oxidation of iodide and iodination of tyrosine. All the steps in the synthesis of thyroid hormones are stimulated by thyroid stimulating hormone (TSH) secreted from the anterior pituitary gland.

T₄ is transported in the blood bound to plasma proteins, mainly T₄-binding globulin and albumin. T₃ is less firmly bound to plasma proteins than T₄. Thyroid hormones are broken down in the liver and skeletal muscle and while much of the iodide is recycled some is lost in the urine and faeces. There is a need, therefore, for daily replacement of iodide in the diet. The half-life of T₄ is 7 days and the half life of T₃ is 1 day.

Control of thyroid hormone secretion

There are two main factors controlling secretion of thyroid hormones. The first is autoregulation of the thyroid which adjusts for the range of iodide in the diet. The other is the secretion of TSH by the anterior pituitary. Other compounds may play a regulatory role such as neurotransmitters, prostaglandins and growth factors but their physiological relevance remains to be demonstrated.

Iodide supply is monitored through its effects on the plasma level of thyroid hormone and in the thyroid itself, where it depresses the response of the thyroid cells to TSH. Large doses of iodine inhibit

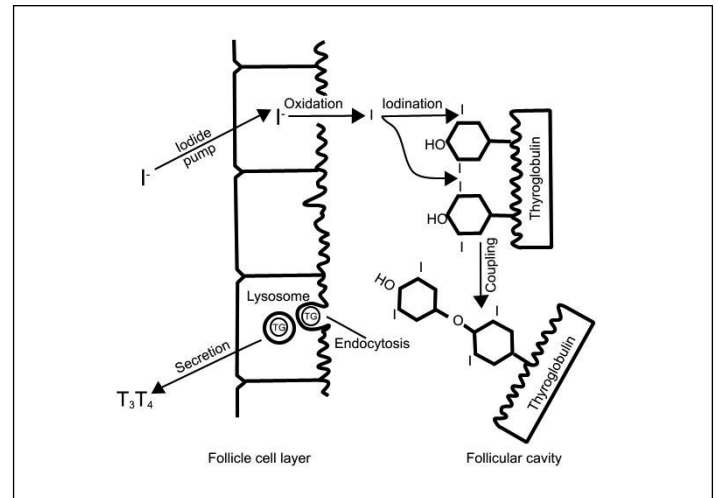


Figure 7. Synthesis of thyroid hormones (T₃, T₄) and their storage in association with thyroglobulin secretion

the release of thyroglobulin bound hormones and thereby reduce the vascularity of the gland. For this reason, iodine has been given to hyperthyroid patients before surgery.

Thyroid hormone plasma levels and action are monitored by the supraoptic nuclei in the hypothalamus and by cells of the anterior lobe of the pituitary. Thyrotrophin-releasing hormone (TRH) is transported from the hypothalamus to the pituitary via the hypophyseal portal vessels and stimulates the secretion of TSH. Rising levels of T₃ and T₄ reduce the secretion of TRH and TSH - negative feedback mechanism (Figure 8).

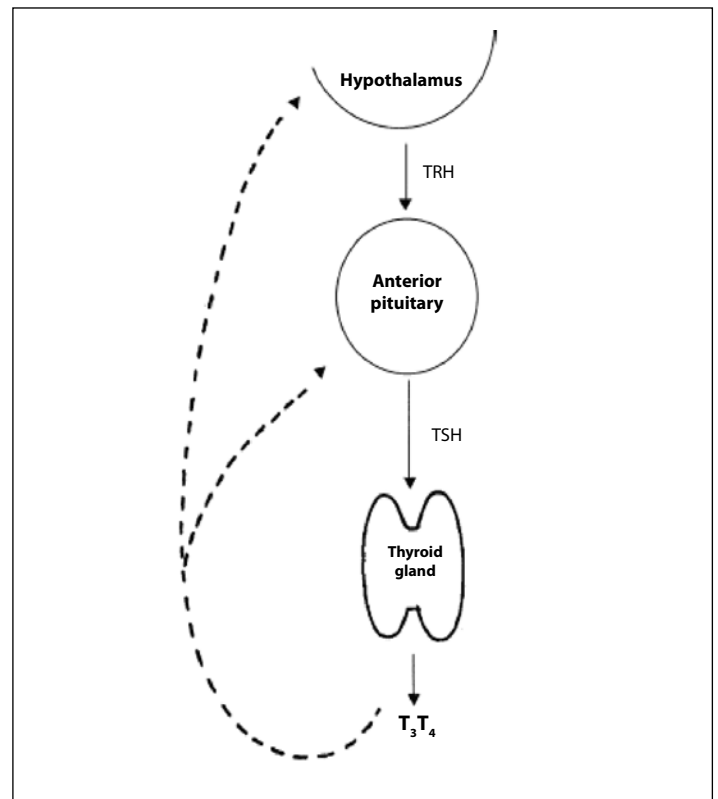


Figure 8. Control of thyroid hormone secretion

Actions of thyroid hormones

Thyroid hormones exert their effects by binding to specific receptors in the nuclei of cells in target tissues. They are involved in metabolism, thermogenesis, growth, development and myelination in childhood.

Oxidative metabolism, basal metabolic rate and therefore heat production is stimulated by T₃ and T₄. They are essential for normal growth in childhood and neonatal deficiency results in severe mental retardation (cretinism). Classical symptoms and signs of hypothyroidism include cold intolerance, lethargy, obesity, hoarseness, bradycardia and a low metabolic rate. Overproduction of thyroid hormones results in hyperthyroidism which is characterised by heat intolerance, loss of weight, hyperexcitability, tachycardia and exophthalmos. An enlarged thyroid gland, or goitre, may be associated with hyperthyroidism (Graves disease) and retrosternal extension of the goitre may cause tracheal compression.

ADRENAL PHYSIOLOGY

The adrenal glands are complex multi-functional organs whose secretions are required for maintenance of life. Failure of the adrenal glands leads to derangement in electrolyte and carbohydrate metabolism resulting in circulatory collapse, hypoglycaemic coma and death.

Each adrenal gland is situated on the superior aspect of each kidney and consists of two endocrine organs (Figure 9). The inner adrenal medulla is mainly concerned with the secretion of the catecholamines epinephrine (adrenaline), norepinephrine (noradrenaline), and dopamine in response to nerve impulses that pass along the preganglionic sympathetic nerves. The outer cortex secretes the steroid hormones, the glucocorticoids, mineralocorticoids and the sex hormones.

The adrenal cortex and medulla have separate embryological origins. The medullary portion is derived from the chromaffin ectodermal cells of the neural crest, which split off early from the sympathetic ganglion cells, while cells of the adrenal cortex are derived principally from coelomic mesothelium.

The adrenal glands are very vascular, the arterial blood supply coming from branches of the renal and phrenic arteries and the aorta. The medulla receives blood from the cortex rich in corticosteroids, which regulate the synthesis of the enzymes that convert norepinephrine to epinephrine. Venous drainage is mainly via the large adrenal vein into either the renal vein or inferior vena cava.

ADRENAL MEDULLA

The adrenal medulla is a modified sympathetic ganglion made up of densely innervated granule containing cells and constitutes about 30% of the mass of the adrenal gland. Approximately 90% of cells are epinephrine secreting cells while the other 10% are mainly the norepinephrine secreting cells. It is still unclear as to which type of cells secrete dopamine. Small collections of chromaffin cells are also located outside the medulla, usually adjacent to the chain of sympathetic ganglia.

Synthesis of hormones

The pathways for the biosynthesis of dopamine, norepinephrine and epinephrine are shown in Figure 10. They are stored in

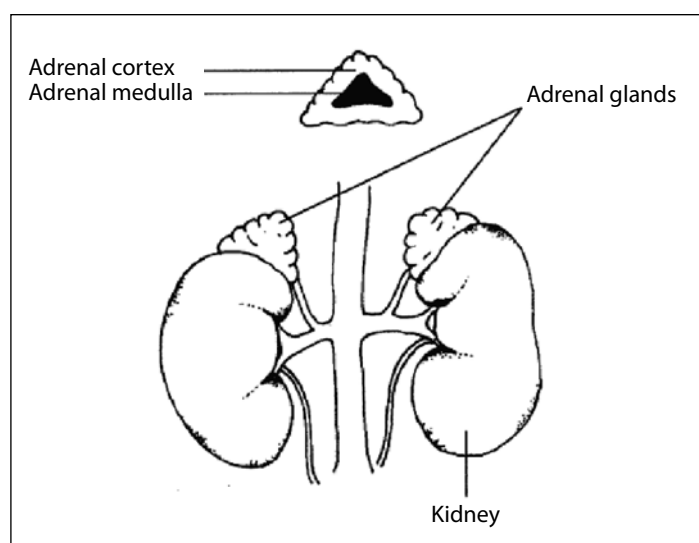


Figure 9. *The adrenal glands*

membrane-bound granules and their secretion is initiated by the release of acetylcholine from sympathetic nerve fibres that travel in the splanchnic nerves. Catecholamines have an extremely short half-life in the plasma of less than two minutes. Clearance from the blood involves uptake by both neuronal and nonneuronal tissues where they are either recycled or degraded by either monoamine oxidase or catechol-O-methyltransferase. About 50% of the secreted catecholamines appear in the urine as free or conjugated metanephrines and normetanephrines and about 35% as vanillylmandelic acid (VMA).

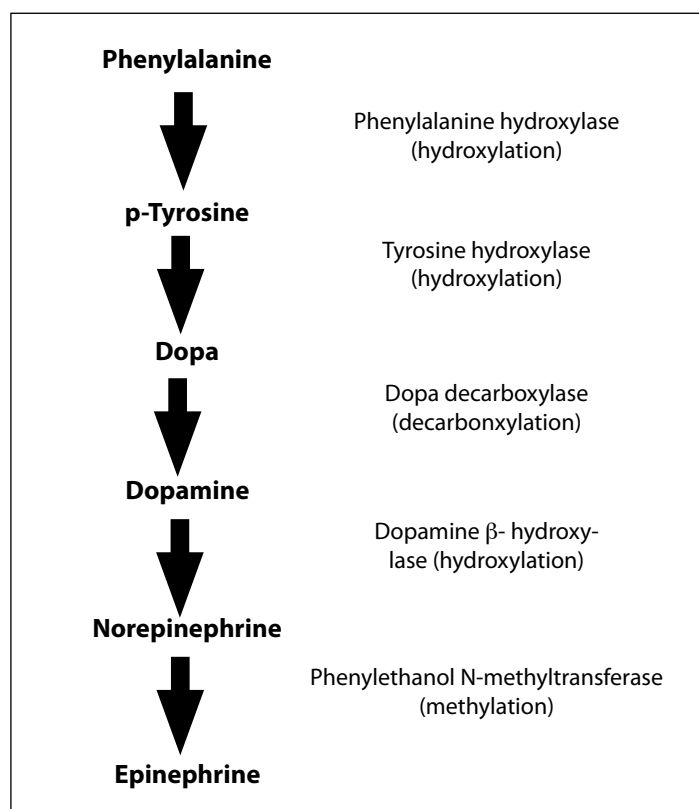


Figure 10. *Catecholamine synthesis*

Effects

The actions of norepinephrine and epinephrine are numerous and complex and depend on their binding to α (α_1 , α_2) and β (β_1 , β_2) adrenergic receptors, while dopamine also acts at specific dopaminergic receptors. The individual actions at these receptors are beyond the scope of this article. They mimic the effects of noradrenergic nervous discharge, stimulate the nervous system, and exert metabolic effects that include glycogenolysis in the liver and skeletal muscle, mobilisation of free fatty acids, increase plasma lactate and increase the metabolic rate. Norepinephrine causes a marked increase in peripheral vascular resistance as a result of widespread vasoconstriction, while epinephrine causes vasoconstriction in skin and viscera but vasodilatation in skeletal muscle so that total peripheral resistance may decrease. While the direct effect of both is an increase in heart rate, the administration of norepinephrine results in reflex bradycardia due to the marked increase in peripheral resistance and mean arterial pressure. They increase alertness, although in humans epinephrine frequently evokes anxiety and fear.

Control of adrenal medullary secretions

Catecholamine secretion is low in basal states and is further reduced during sleep. Secretion is initiated by sympathetic activity controlled by the hypothalamus and occurs in response to pain, anxiety, excitement, hypovolaemia and hypoglycaemia. With emergency stimulation you get diffuse medullary secretion preparing the person for the fight or flight response.

Disorders of adrenomedullary function

Phaeochromocytomas arise from chromaffin cells in the adrenal medulla and in other paraganglia of the sympathetic nervous system. They are usually benign tumours and the clinical features depend on the activity of the tumour and the relative amounts of epinephrine and norepinephrine secreted. Typical signs and symptoms may include hypertension, hyperglycaemia, headache, palpitations, sweating, pallor and nausea. Definitive treatment generally involves surgical removal of the tumour.

ADRENAL CORTEX

The adrenal cortex is responsible for the secretion of the glucocorticoids, mineralocorticoids and androgens (sex hormones). Glucocorticoids affect the metabolism of carbohydrates, fats and proteins and are important in mediating the response to fasting and stress. Mineralocorticoids are essential for sodium balance and consequently extracellular fluid balance. Androgens have a minor role in reproductive function when compared to the pituitary hormones, FSH and LH. Histologically the adrenal cortex is divided into three distinct layers. The outermost layer contains the cells of the zona glomerulosa, the middle layer, the largest layer, contains the cells of the zona fasciculata, while the innermost layer contains the cells of the zona reticularis. All three zones secrete corticosterone, while in contrast, aldosterone biosynthesis occurs in the zona glomerulosa. The enzyme mechanism for forming cortisol (hydrocortisone) and androgens is mainly found in the two inner zones.

Synthesis

The hormones produced by the adrenal cortex contain the cyclopentanoperhydrophenanthrene nucleus with the glucocorticoids

and mineralocorticoids containing 21 carbon atoms and the androgens 19. The precursor of all steroid hormones is cholesterol. ACTH releases cholesterol from lipid droplets in the cytoplasm of the cells. It is converted in the mitochondria to pregnenolone. This is the rate-limiting step in the biosynthesis of the steroidal hormones and is again regulated by ACTH. The pregnenolone is then transferred to the smooth endoplasmic reticulum where it undergoes further modification to form the three main classes of steroids. The actions of ACTH are thought to be mediated by cyclic-AMP. While several steroids have been identified, the steroids that are secreted in clinically significant amounts are aldosterone, the glucocorticoids cortisol and corticosterone, and the androgens dehydro-epiandrosterone and androstenedione. The adrenal glands can also produce small amounts of estrogens.

The corticosteroids in the circulation are mainly bound to plasma proteins such as corticosteroid-binding globulin (transcortin) and albumin. Inactivation of the hormones occurs mainly in the liver where they are conjugated with glucuronic acid or sulphate and excreted in the urine.

Actions of glucocorticoids

Glucocorticoids play a vital role in the control of carbohydrate, fat and protein metabolism. They promote glycogen storage in the liver. During fasting they promote gluconeogenesis in the liver to provide glucose for brain metabolism. They are counter-regulatory to insulin, resulting in elevated blood glucose. Glucocorticoids potentiate the vasoconstrictor effects of catecholamines and decrease the permeability of vascular endothelium which is essential for maintenance of normal vascular function. Cortisol release increases during stress, and in patients with adrenocortical insufficiency absence of this response can result in hypotension and death. The glucocorticoids also have some mineralocorticoid activity. They have been shown to have anti-inflammatory properties and can suppress the immune response.

Regulation of adrenal cortical function

Secretion of the glucocorticoids is controlled by ACTH produced by the anterior pituitary (Figure 5). This is controlled by the hypothalamic secretion of corticotropin-releasing hormone (CRH) into the hypophyseal portal system. The release of cortisol exerts a negative feedback effect on both the anterior pituitary and the hypothalamus. Plasma cortisol levels follow a diurnal pattern, peak levels occurring in the morning just before waking.

Actions of mineralocorticoids

Aldosterone and the other steroids with mineralocorticoid activity (corticosterone, deoxycorticosterone) increase the reabsorption of sodium acting mainly on the distal tubules of the kidney, resulting in the retention of sodium in extracellular fluids. Sodium is in effect exchanged for potassium and hydrogen, resulting in a potassium diuresis and acidic urine. In adrenal insufficiency, sodium is lost in the urine while potassium is retained resulting in raised plasma potassium. Plasma volume may also be reduced, resulting in hypotension and circulatory insufficiency. The renin-angiotensin system has a major role in the maintenance of blood volume and electrolyte balance.

Regulation of aldosterone secretion

The main factors regulating aldosterone secretion are the renin-angiotensin system, ACTH from the pituitary, and the effects of a rise in plasma potassium or a fall in plasma sodium, which result in a direct stimulatory effect on the adrenal cortex.

Aldosterone is only one of many factors affecting sodium secretion. Other major factors include the glomerular filtration rate, atrial natriuretic peptide (ANP) and changes in tubular reabsorption of sodium independent of aldosterone. It is likely that the primary function of the aldosterone secreting mechanism is in the maintenance of the intravascular volume, although there are several other mechanisms involved.

Disorders of adrenocortical function

Cushing's syndrome is the result of excess corticosteroids, the commonest cause being prolonged treatment with relatively large doses. Apart from the iatrogenic causes this disorder is very rare, other causes being primary tumours of the adrenal gland, adenoma or hyperplasia of the pituitary gland. In addition Cushing's syndrome can be secondary to carcinomas elsewhere, such as oat cell carcinoma of the lung, due to uncontrolled ACTH secretion, the 'ectopic ACTH syndrome'. Conn's syndrome is also very rare, caused by a benign adenoma or hyperplasia of the zona glomerulosa producing excess aldosterone.

Acute adrenal insufficiency can occur after trauma, severe hypotension and sepsis. It may follow surgical removal of the adrenals unless there is adequate replacement therapy. Chronic adrenal insufficiency (Addison's disease) occurs when there is destruction of the adrenal

gland, caused by autoimmune disease, secondary tumour infiltration, tuberculosis or amyloidosis.

Excess androgen secretion causes masculinisation (adrenogenital syndrome). This can result from an androgen secreting adrenocortical tumour or due to a congenital enzyme defect affecting cortisol synthesis. In the latter case, the resulting decrease in circulating cortisol stimulates the overproduction of ACTH, which in turn stimulates the adrenals to produce excess androgenic steroids. Females show signs of virilisation while males show precocious puberty. Extreme feminisation in males can occasionally be due to an oestrogen-producing tumour of the adrenal gland.

CONCLUSION

The anaesthetist should, have a basic understanding of the physiology of the pituitary, thyroid and adrenal when involved with the management of patients with endocrine disease. Furthermore, this knowledge is fundamental to understanding the metabolic changes that occur following the stress of surgery.

FURTHER READING

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Table 2. Summary of the more common disorders of adrenocortical function

Hormone	Syndrome	Symptoms and Signs
Glucocorticoid excess	Cushing's syndrome	Moon facies, truncal obesity, buffalo hump, abdominal striae, muscle weakness and wasting, hypertension, diabetes mellitus, hypokalaemia and metabolic alkalosis.
Mineralocorticoid excess	Conn's syndrome	K ⁺ depletion, Na ⁺ retention, polyuria and hypokalaemic alkalosis, hypertension, tetany and weakness.
Adrenocortical insufficiency (Adrenocortical atrophy due to autoimmune diseases or diseases of the adrenal gland)	Addison's disease	Skin pigmentation, Na ⁺ depletion, decreased plasma volume, weakness, tiredness and weight loss.
Adrenal androgen excess (Androgen secreting tumour, or congenital)	Adrenogenital syndrome Congenital adrenal hyperplasia	<i>In female:</i> hirsutism, acne, oligomenorrhea & virilisation <i>In male:</i> precocious puberty.

Renal Physiology

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INTRODUCTION

The kidney is a complex organ with several different functions. One way to remember these functions is to think about a patient who has chronic renal failure. The main features are:

1. Salt and water retention with oedema and hypertension
2. Uraemia
3. Hypercalcaemia and hyperphosphataemia
4. Acidosis and hyperkalaemia
5. Anaemia.

The main functions of the kidney are therefore:

1. Salt and water balance or homeostasis
2. Toxin removal
3. Calcium and phosphate homeostasis
4. Acid-base homeostasis
5. Stimulation of erythropoiesis

Homeostasis means 'maintenance of the internal environment' of the body within closely regulated limits. The functions of the kidneys are necessary to maintain this constant environment despite great variation in oral intake and the external environment.

BASIC STRUCTURE OF THE KIDNEYS

The kidney has several layers starting from the outer renal cortex moving deeper to the outer medulla and then to the inner medulla. The specialised structure within the kidney is the nephron. Each kidney contains approximately one million nephrons. Each nephron consists of:

- A glomerulus, which in turn consists of a capillary tuft and a specialised enclosed pouch

like extension of the tubule called the Bowman's capsule

- The proximal convoluted tubule (PCT)
- The descending thin limb of the loop of Henle
- The ascending thin and thick limb of the loops of Henle
- The vasa recta, which is a series of specialised capillaries which wrap around the loop of Henle
- The distal convoluted tubule (DCT)
- The collecting duct.

The glomeruli sit within the renal cortex and drain into the PCT. This then drains into the descending limb of the loop of Henle, which descends down through the medulla. It then turns back on itself, becoming the ascending limb, and returns to the cortex before becoming the DCT. The DCT drains

Summary

The major functions of the kidneys can be identified by knowledge of the pathological changes seen in renal failure. The kidney has important roles in salt and water, acid-base, electrolyte and calcium homeostasis. These functions are described, including the role of the countercurrent multiplier and exchange systems of the loop of Henle. Where relevant, clinical examples are used to demonstrate the multiple roles of the kidney.

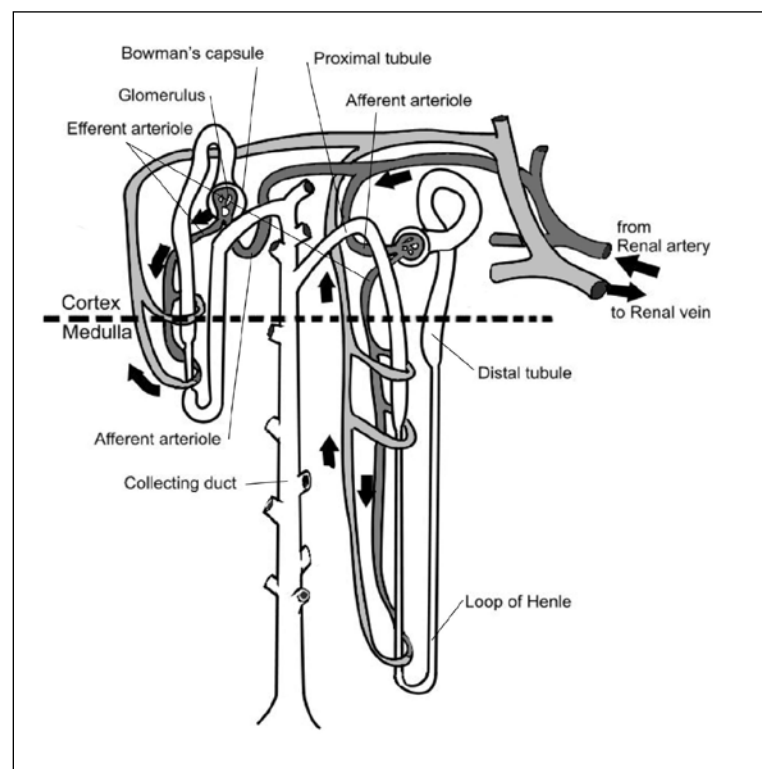


Figure 1. Detailed anatomy of the kidney and nephron

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into a collecting duct which descends back down through the medulla so that urine can drain into the renal pelvis and ureter. Humans have a mixture of short (cortical nephrons) and long (juxta-medullary) nephrons - eighty-five per cent are short in humans. In general the greater the proportion of long loops or length of loop the greater the concentrating ability (for example dogs are able to concentrate urine to greater than 3000mosm.l⁻¹, and some desert animals to greater than 5000 mosm.l⁻¹)

FUNCTIONS OF THE KIDNEY

Glomeruli

The glomerulus is the filter unit of the nephron. It passively lets water, amino acids, sodium and other free ions pass through its membranes and into the tubule system, but not charged proteins, large proteins or cells. The unique basement membrane, which is at the interface of the capillaries and Bowman's capsule, allows this to happen. Glomerular filtration produces up to 125ml filtrate per minute, most of which needs to be quickly reabsorbed.

Proximal convoluted tubule (PCT)

The PCT is responsible for the majority of the reabsorption. There are four different mechanisms by which solute transport occurs:

1. *Passive diffusion* which occurs across a membrane down an electrochemical gradient, e.g. sodium and chloride ions.
2. *Facilitated diffusion* which is also passive but is more selective as it requires the interaction between an ion and a membrane-bound specific carrier protein, e.g. sodium/amino acid cotransporter.
3. *Passive diffusion through a membrane channel or pore*, e.g. potassium in the collecting duct.
4. *Active transport* against an electrochemical gradient by an energy requiring pump, e.g. the potassium-hydrogen ion antiporter in the collecting duct.

Some transporters within the PCT are responsible for secretion of weak acids and bases. As drugs can be weak acids or bases (e.g.

diuretics) this is one of the renal mechanisms for eliminating drugs from the body. The majority of renal elimination of drugs from the body however is by filtration.

Loop of Henle

The human body has no active pump for water, which can only move across a membrane by osmosis. The role of the Loop of Henle is to create an increasing concentration gradient in the interstitial tissues as the loop passes deeper into the medulla. A gradient from about 285mosm.l⁻¹ in at the beginning of the loop to 1200mosm.l⁻¹ at the apex of the loop is achieved. The collecting ducts pass through this osmotic gradient and so, under the influence of antidiuretic hormone (ADH), water can be retained. The loops of Henle constitute a countercurrent system - the ascending and descending limbs of each loop are parallel, counter to (i.e. opposite in flow) and in close proximity to each other.

There are 3 sections to the loop of Henle:

1. Thin descending limb
2. Thin ascending limb
3. Thick ascending limb

The countercurrent system consists of:

- *A countercurrent multiplier* (the loop of Henle) which sets up an increasing gradient of osmolality as you go to the bottom of the loop.
- *A countercurrent exchange* (the vasa recta) which maintains this gradient. ADH acts to allow uptake of water from the collecting ducts. The osmotic gradient would otherwise gradually diminish as water is reabsorbed by osmosis.

Countercurrent multiplier

Essentially, sodium and chloride (Na⁺ and Cl⁻) leave the ascending limb, which is impermeable to water which therefore cannot follow. Deep in the medulla, Na⁺ and Cl⁻ leave by passive diffusion, however this passive diffusion is not sufficient to maintain such a steep gradient, so in the thick ascending limb sodium is actively pumped out into the interstitium. Water *does* move out of the descending limb into the interstitium by osmosis and this leaves the fluid within the descending limb gradually increasing in osmolality as it moves deeper into the medulla towards the apex of the loop.

It is only as tubular fluid enters the ascending loop that it starts to become less concentrated as Na⁺ and Cl⁻ are actively pumped out (which is where we started). In effect, Na⁺ and Cl⁻ are circulating around the bottom part of the loop which generates the high osmolality in the interstitium.

Countercurrent exchange

The multiplier is self-perpetuating until ADH allows water to be reabsorbed, thereby lowering the osmolality in the interstitium. The vasa recta are also countercurrent in their lay-out and they act in a very similar way to maintain the hypertonicity of the interstitium at the bottom of the loop.

Table 1. Substances reabsorbed in the PCT

Substance	Approximate % reabsorbed in PCT
Water	65
Sodium	60
Potassium/Chloride/Bicarbonate	80
Glucose	100
Amino acids	100
Calcium	60
Phosphate	80
Urea	50

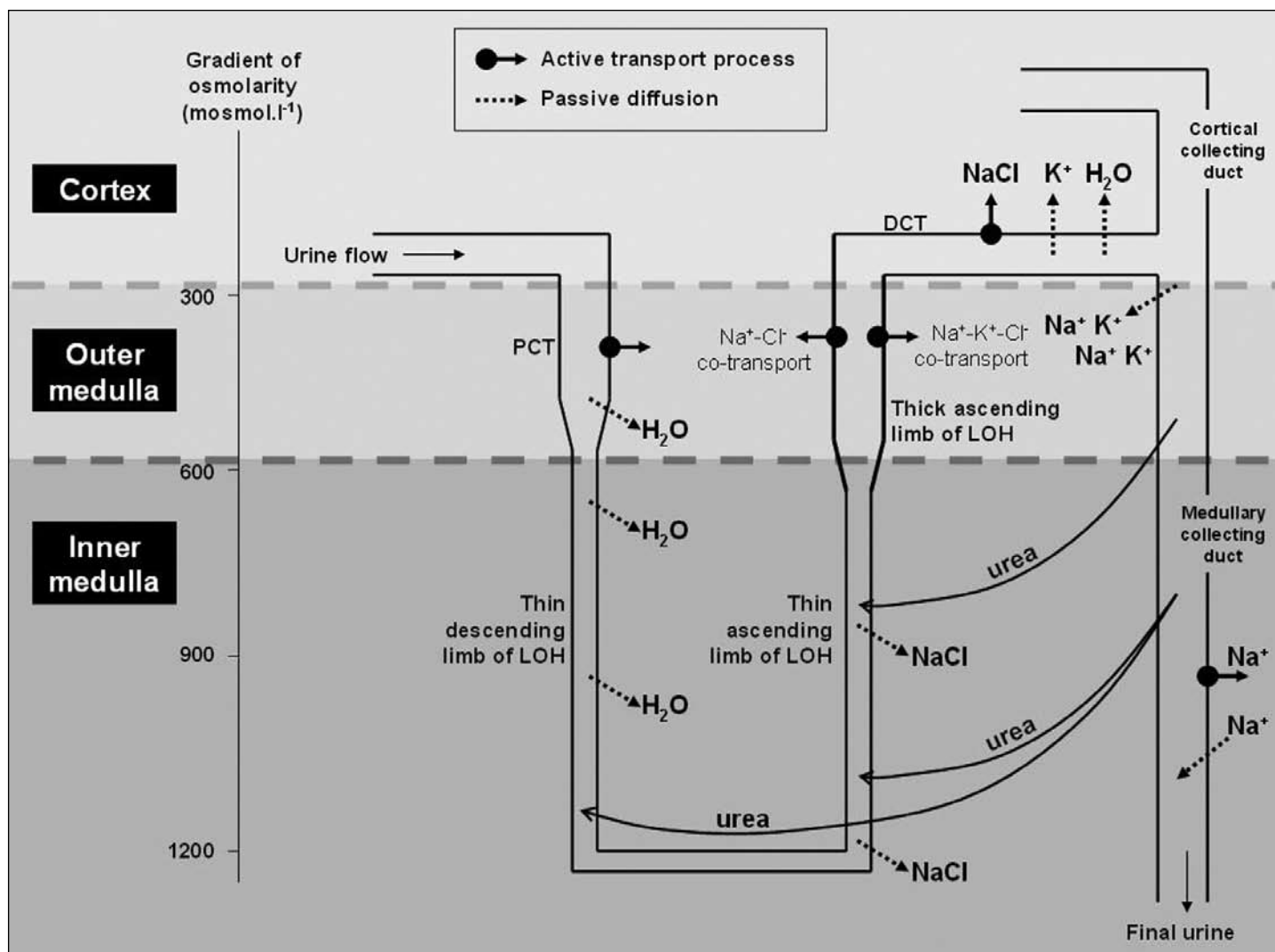


Figure 2. The function of the loop of Henle in concentration of urine

Na^+ and Cl^- diffuse from the ascending vasa into the descending vasa and recirculate around the lowest parts of the loops. At the same time water diffuses from the descending vasa across to the ascending vasa.

The role of urea

The other major factor in generation of the hypertonic medulla is the fact that the collecting ducts are impermeable to urea until the portions deep within the medulla, by which time (after water reabsorption) the urea concentration is very high. When urea reaches this part of the collecting duct, ADH sensitive urea channels allow it to move into the interstitium down a concentration gradient and this further increases the osmolality of the interstitium. Some of the urea diffuses back into the filtrate in the thin limbs of the loop of Henle and some stays within the interstitium.

In summary the important points about the counter current multiplier system are:

1. It is driven by the active reabsorption of the sodium in the thick ascending limb.

2. Different segments of the loop have different permeabilities to water and sodium.
3. Reabsorbed water is rapidly removed from the interstitium into the systemic circulation via the vasa recta.
4. Sodium which is reabsorbed is effectively 'trapped' in the interstitium.
5. The ascending and descending limbs of the same nephron run parallel to each other with the filtrate running in opposite directions.
6. The unique arrangement of the blood supply (the vasa recta) is an essential component in this system.

Distal convoluted tubule (DCT)

The DCT is where the final fine tuning of the reabsorption of many ions such as sodium, calcium, phosphate, potassium, and acid base balance is achieved.

Collecting duct

The collecting duct passes down through the concentration gradient

generated by the countercurrent system. It has varying permeability to water depending on the amount of antidiuretic hormone present and therefore is responsible for concentrating urine. It is also involved with acid secretion (see below)

RENAL BLOOD FLOW

Twenty per cent of the cardiac output (about 1200ml.min⁻¹) goes to the kidney. The amount of blood flow directly affects the rate at which the glomerulus can filter (the glomerular filtration rate - GFR) and subsequently the amount of filtrate produced.

Rate of removal = blood flow to organ x arteriovenous difference (a-v) of substance in concentration of substance

So to measure renal plasma flow a substance with high extraction is used, for example para-amino hippuric acid (PAH):

Rate of removal in urine (u) = urine concentration x urine volume

Venous concentration is close to zero, so a-v = a

So renal plasma flow (RPF) = $\frac{u \times v}{a} \times \frac{1}{0.9}$

(PAH has an extraction ratio of 90%)

For renal blood flow, multiply by $\frac{1}{1 - \text{haematocrit}}$

Similarly for glomerular filtration rate (GFR), choose a substance which is freely filtered at the glomerulus and neither secreted or re-absorbed, e.g. inulin or creatinine.

GFR = clearance of inulin = $\frac{u \times v}{p}$ where p = plasma concentration

The filtration fraction = $\frac{\text{GFR}}{\text{RPF}} = 0.16-0.2$

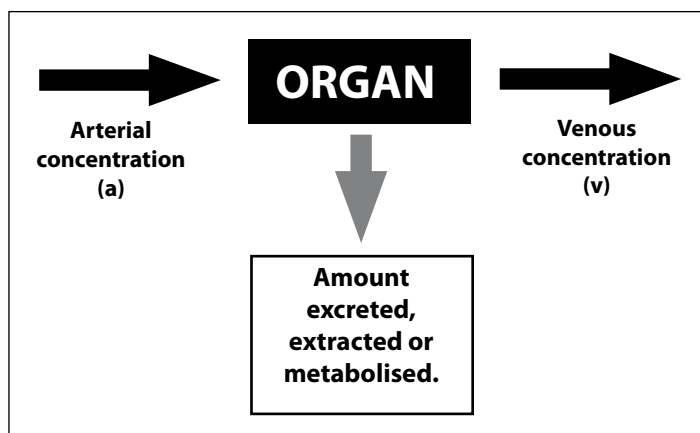


Figure 3. The Fick principle can be used to calculate blood flow for any organ system using a substance that is removed (excreted, extracted or metabolised) by the organ

The blood flow into the glomerulus is via the afferent arteriole and the blood flow out of the glomerulus is by the efferent arteriole.

Altering the radius of either or both of these vessels will alter the pressure within glomerulus. This is called autoregulation, and is achieved with the help of the macula densa, a group of specialised cells which sit within the distal part of the ascending limb of the loop of Henle. They are also in close proximity to the afferent and efferent arterioles. The capillaries and the macula densa together make up the juxtaglomerular complex. If the blood pressure falls there is a decrease in the renal blood flow, and a decreased volume of filtrate. This causes a decreased delivery of sodium and chloride to the macula densa. The macula densa senses this and stimulates the local release of a hormone, renin. Renin converts circulating angiotensinogen to angiotensin I. Angiotensin I is carried to the lungs where it is converted to angiotensin II by angiotensin converting enzyme (ACE). Angiotensin II is then taken back into the systemic circulation and has its effects as outlined in Figure 4.

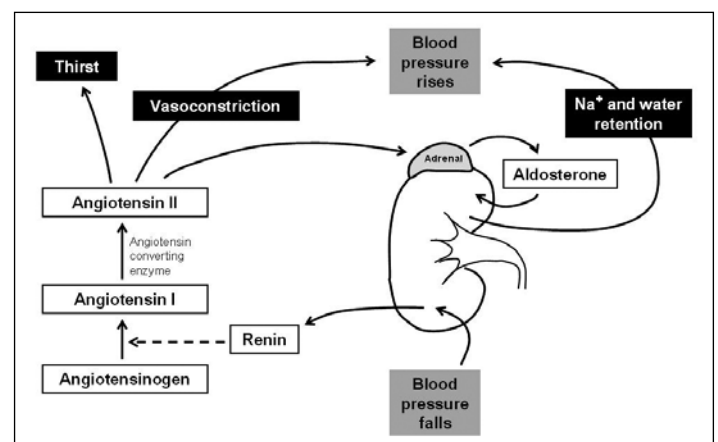


Figure 4. The renin-angiotensin system

Clinical points

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin production and so can impair afferent arteriolar dilatation, reducing GFR. It is for this reason that NSAIDs should be avoided in patients with renal impairment and those who are hypovolaemic and reliant on afferent vasodilatation to maintain GFR.

Patients with *renal artery stenosis* rely on high efferent arteriolar tone to maintain a high filtration pressure across the glomerulus. *ACE inhibitor drugs* are contraindicated in these patients since they inhibit efferent arteriolar constriction (by inhibiting angiotensin II production) and so GFR is dramatically reduced, with consequent deterioration in renal function.

The angiotensin II has four effects:

1. Generalised vasoconstriction causing increased systemic vascular resistance and increasing the blood pressure.
2. Constriction of both the afferent and efferent arteriole but constricting the efferent more. This then increases the differential pressure across the glomerular capillary tuft and increases the GFR.
3. Stimulation of the release of aldosterone from the adrenal gland, which stimulates the reabsorption of sodium from the DCT and collecting duct.

4. Stimulates thirst via an action on the hypothalamus.

Other substances such as nitric oxide and prostaglandins which vasodilate are also released locally in response to altered pressure within the capillary tuft, but the exact mechanisms are poorly understood.

WATER HOMEOSTASIS

Water balance is controlled by antidiuretic hormone (ADH). ADH is released from the posterior pituitary in response to three stimuli:

1. Increased osmolality in the hypothalamus,
2. Decreased plasma volume (cardiopulmonary receptors in the right atrium and pulmonary vessels),
3. Angiotensin II.

Osmoreceptors located in the hypothalamus sense an increase in plasma osmolality and stimulate the release of ADH. Reduced blood pressure is sensed by the atrial stretch receptors and arterial baroreceptors, which also stimulate the release of ADH. ADH release causes an increase in the number of water channels called aquaporins, with in the collecting duct. This facilitates greater water reabsorption by osmosis, as the collecting ducts pass through the concentration gradient generated by the loop of Henle.

SODIUM BALANCE

Approximately 60% of sodium is reabsorbed in the PCT, 20% in the loop of Henle and 5% in the DCT and collecting duct.

There are several mechanisms by which sodium reabsorption or excretion can be affected. The most important are:

1. The renin–angiotensin–aldosterone system
2. Atrial natriuretic peptide

One of the end points of the activation of the renin-angiotensin system is the release of aldosterone. Aldosterone increases sodium reabsorption by increasing the number of sodium channels and the sodium pumps which drive the reabsorption of sodium in the DCT and the collecting duct.

Atrial natriuretic peptide is released in response to atrial stretch, a sign of salt and water overload. This increases the sodium excretion by inhibiting the renin-angiotensin system (see above) and by direct inhibition of the reabsorption of sodium in the collecting duct.

POTASSIUM BALANCE

Potassium is freely filtered by the glomerulus. Almost all of it is then reabsorbed by the PCT. The mechanism at this point is not regulated and does not respond to differing plasma potassium concentrations. The DCT and collecting ducts are responsible for regulating potassium balance by increasing secretion or reabsorption.

There are two clinically important mechanisms for potassium exchange. Aldosterone stimulates potassium secretion by increasing sodium reabsorption. Sodium is reabsorbed in exchange for potassium by an active transporter. Thus drugs such as spironolactone which antagonise aldosterone can cause hyperkalaemia.

Box 1. ADH and the renin-angiotensin systems are demonstrated by the body's response to different haemodynamic challenges:

1000ml 0.9% saline intravenously - a response to a small increase in volume

This is a volume load but it is isotonic. The volume expansion is initially 1000ml which distributes quickly into the extracellular fluid - about 250ml stays in the intravascular volume, the remainder fills the interstitial space:

- ↑ blood volume stimulates cardiopulmonary stretch receptors (right atrium)
- posterior pituitary → ↓ ADH secretion
- ↓ thirst and diuresis

1000ml blood intravenously - a response to a large increase in volume

This volume stays in the intravascular compartment.

Acute response

- stimulates the baroreceptors of the arterial system (carotid & aortic sinuses)
- via the glossopharyngeal and vagus nerves
- reflex ↓ cardiac output and ↓ vascular tone

Slower response

- ↓ activation of renin-angiotensin system
- ↓ aldosterone secretion

1000ml 5% glucose intravenously or water orally - a response to a decrease in osmolality

This constitutes less of a volume load since it is distributed into the entire body water. One twelfth stays in the intravascular space (83ml). Oral water is similar since it is rapidly absorbed from the stomach. However it does cause plasma dilution and ↓ osmolality:

- detected by osmoreceptors of the hypothalamus
- ↓ ADH secretion

The response to hypokalaemia in the collecting duct is to stimulate the uptake of potassium from the filtrate by activating the potassium ion-hydrogen ion exchange pump. This secretes hydrogen ions into the collecting duct in exchange for reabsorbing potassium ions. This is why hypokalaemic patients are often alkalotic. This pump is also stimulated by acidosis and is one of the reasons why acidotic patients are often hyperkalaemic.

The kidney can maintain normal serum potassium concentration down to low GFRs. When the kidneys potassium handling ability finally fails the patient becomes hyperkalaemic due to the low quantities of blood being filtered and the inability of the kidney to respond by secreting increased levels of potassium. Faecal excretion of potassium is up-regulated to help maintain serum potassium as the kidney fails.

TOXIN REMOVAL

Toxins are removed by two mechanisms:

1. Filtration
2. Secretion

Most water soluble toxins such as creatinine are freely filtered and not reabsorbed. Therefore the levels should remain constant and at non-toxic levels in the blood unless ingestion, production or GFR changes.

Some toxins are removed from the blood by active secretion in the PCT. Drugs such as diuretics and trimethoprim are removed in this way.

CALCIUM AND PHOSPHATE HOMEOSTASIS

The kidney plays a major role in calcium homeostasis, along with the skeleton and intestine. The intestine allows calcium and phosphate to be absorbed from the diet. The skeleton is the store of calcium. The kidney has two roles:

1. The activation of vitamin D (via addition of a second hydroxyl group) which then facilitates calcium absorption from the digestive tract.
2. The tubular reabsorption and excretion of calcium and phosphate respectively under the influence of parathyroid hormone.

Vitamin D stimulates the absorption of both calcium and phosphate from the intestine and is part of the feedback mechanism which controls plasma levels of these ions.

ACID BASE BALANCE

Maintenance of a constant pH is very important for the body as many of our enzyme systems are very pH sensitive. Both acids and alkalis are generated from the diet either by direct ingestion or by generating an acid or an alkali after metabolism. There is usually a net acid production.

Bicarbonate is the main buffer in the human body. As almost 100% of bicarbonate is filtered by the kidney, to help maintain the pH in the body the bicarbonate must be reabsorbed. This is mainly done by the PCT which acidifies the urine. The pH falls from 7.3 to 6.7 along the length of the PCT.

The PCT reabsorbs bicarbonate by secreting hydrogen ions into the lumen of the tubule. The enzyme carbonic anhydrase catalyses the conversion of the hydrogen ion and the bicarbonate ion into water and carbon dioxide with in the tubule. The carbon dioxide then diffuses back into the cell where carbonic anhydrase catalyses the

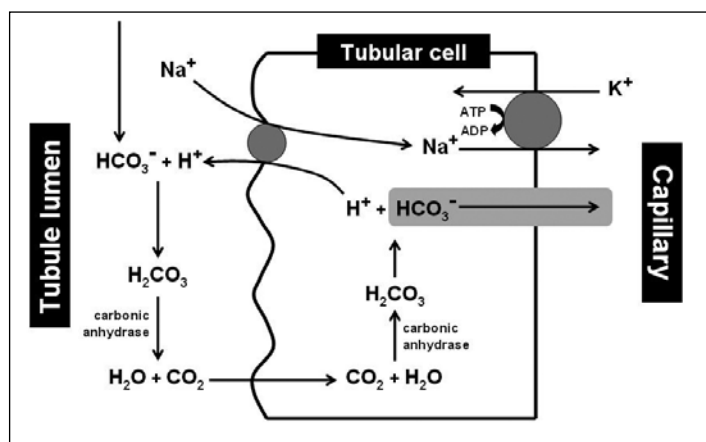


Figure 5. Bicarbonate reabsorption in the PCT

reverse - carbon dioxide combines with water to form bicarbonate, which is reabsorbed into the blood stream, and a hydrogen ion, which is recycled to be used to reabsorb another bicarbonate ion. The mechanism of bicarbonate reabsorption does not cause a net loss of hydrogen ions and does not excrete any of the acid produced by the body.

The distal nephron then reclaims any of the bicarbonate that remains in the filtrate after passing through the PCT.

Although when the filtrate reaches the collecting duct it is acidic, this is because of the reabsorption of bicarbonate not the excretion of acid. As stated previously there is an excess of acid generated by metabolism that the body needs to excrete. Although the vast majority is achieved by carbon dioxide excretion by the lungs, an important fraction (particularly phosphate and sulphate ions) is excreted by the collecting duct. Hydrogen ions are actively secreted by the hydrogen ion-potassium ion antiporter (see above). This would result in a sharp increase in the acidity of the urine if the hydrogen ions were not buffered. As all the bicarbonate has been reabsorbed, the hydrogen ions are buffered primarily by ammonia, created from glutamine in the renal tubular cells and filtered phosphate ions.

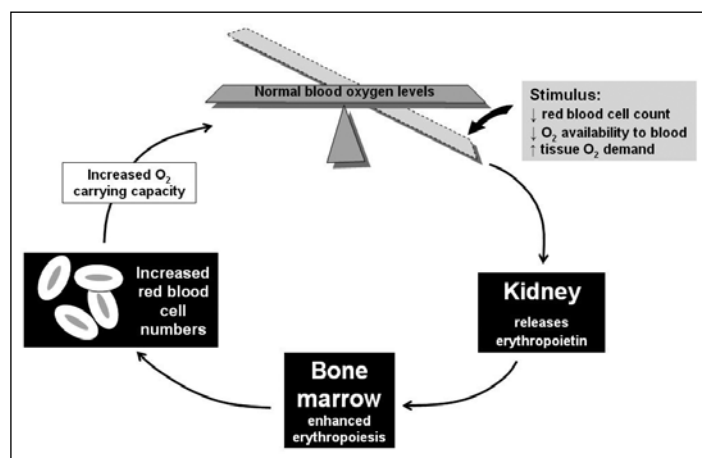


Figure 6. Regulation of erythropoiesis by erythropoietin

ERYTHROPOIESIS

The kidney responds to hypoxia and decreased red blood cell mass (decreased oxygen carrying capacity) by releasing erythropoietin which stimulates the bone marrow to produce more red blood cells (Figure 6).

CONCLUSION

This article provides an overview of the major functions of the kidney. A clear understanding of these concepts is essential for safe administration of drugs during anaesthesia, particularly in those with impaired renal function. A logical knowledge of the physiology of the renal system allows recognition and appropriate management of patients with renal failure, particularly in patients with critical illness.

Liver Physiology

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ANATOMY

The liver weighs 1.5 to 2kg and is divided into right and left lobes, the right lobe being larger than the left. The functional unit of the liver is known as a 'hepatic lobule'. These are roughly hexagonal in cross section and contain a central vein from which cords of hepatocytes radiate outwards (Figure 1). In between the lobules lies the portal triad consisting of hepatic artery, portal vein and bile duct. Radial spaces between the hepatocytes are called sinusoids and carry mixed hepatic arterial and portal venous blood towards centre of the lobule where it drains into the central vein. Central veins join to form the hepatic vein that drains into the inferior vena cava.

Hepatocytes are highly active metabolically and the walls of the sinusoids are also lined by macrophages, known as Kupffer cells, that are an active part of the reticuloendothelial system.

Blood Supply

The liver receives about $1.5\text{ l}\cdot\text{min}^{-1}$ blood supply (about 25% of the total resting cardiac output) and is responsible for over 20% of the body's resting oxygen consumption. It has a dual vascular supply from the portal vein and the hepatic artery. The hepatic artery is a high pressure and high resistance system which deliver 30% of total hepatic blood flow directly from the aorta and contributes to about 50% of total

hepatic oxygen supply. The portal vein is a valveless system, bringing deoxygenated blood from the large and small intestines, spleen, stomach, pancreas and gall-bladder. It contributes to 70% of total liver blood flow and 50-60% of total oxygen supply, containing blood with a saturation of about 85%.

FUNCTIONS OF THE LIVER

The functions of liver may be summarised as:

1. Metabolism of carbohydrates, proteins and fat,
2. Detoxification of drugs and toxins,
3. Storage of glycogen, vitamins (e.g. A,D,E,C), iron and copper,
4. Reservoir of blood,
5. Filtration of bacteria, degradation of endotoxins and lactate metabolism,
6. Excretion of bile and urea,
7. Immunological functions with synthesis of immunoglobulins and phagocytic action by Kupffer cells ,
8. Haemopoiesis in the foetus.

Protein metabolism

The liver has a central role in both protein metabolism and anabolism. It removes amino acids from blood for gluco-neogenesis and protein synthesis. It also releases amino acids into the blood for utilisation by peripheral tissues and plays a major role in breakdown of amino acids, removing nitrogen in the form of urea.

The liver synthesizes many important proteins such as albumin, which is responsible for maintaining colloidal osmotic pressure, globulins such as the lipoproteins and glycoproteins with transport functions. Examples of the latter are ferritin, ceruloplasmin, α_1 antitrypsin, α_2 macroglobulin, complement factors and haptoglobins, which bind and conserve free haemoglobin. It also synthesizes antithrombin-3, α acid glycoprotein and C-reactive protein, which are acute phase proteins, produced under conditions of physiological stress.

Synthesis of almost all clotting factors occurs in the

Summary

The liver has a unique anatomical structure essential to its diverse functions. This article gives an overview of the role of the liver in body metabolism, as well as its relevance to anaesthesia and critical care. Bilirubin metabolism and the causes of jaundice are described.

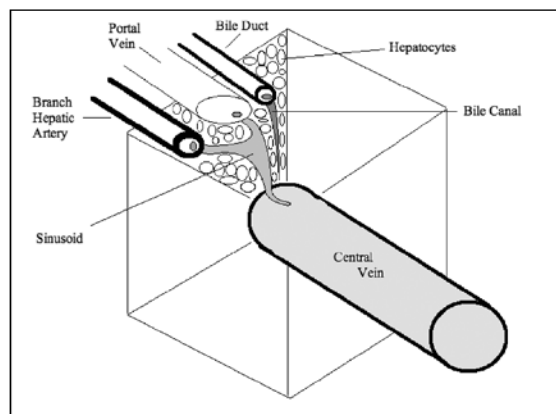


Figure 1. The hexagonal hepatic lobule showing the portal triad of hepatic artery, portal vein and bile duct at the periphery of the lobule and central vein in the centre of the lobule

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liver. Coagulopathies can occur with either failure of hepatic synthesis or failure of bile excretion, leading to a reduction in absorption of vitamin K. Vitamin K is required for the synthesis of factors II (prothrombin), VII, IX and X.

The liver also synthesizes acute phase proteins in response to numerous stimuli.

Protein catabolism

Amino acids degradation is by transamination, deamination and decarboxylation. The products are acetylcoenzyme A, which enters the citric acid cycle. The nitrogenous end-product of amino acid degradation is ammonia. Ammonia is a toxic end product and is eliminated from the body as urea.

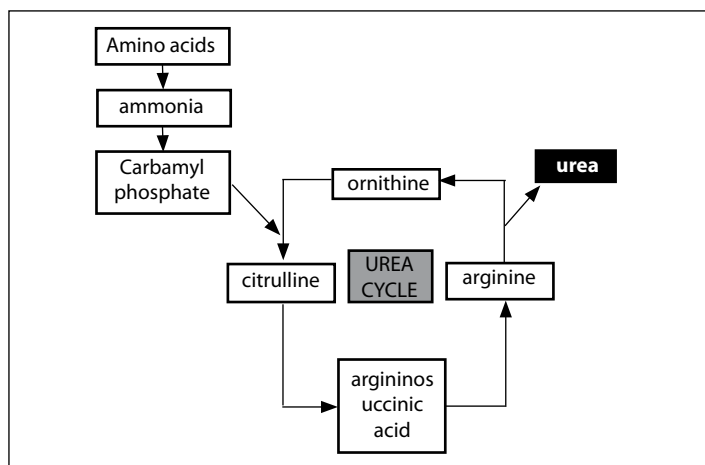


Figure 2. The urea cycle

Urea is synthesized from ammonia by the ornithine cycle, an energy-dependent process (Figure 2). Creatinine is also synthesized in the liver from methionine, glycine and arginine. Phospho-creatine formed in the muscle is a back-up energy store for ATP production. Creatinine is formed from phospho-creatine and is excreted in urine.

Carbohydrate metabolism

The liver maintains glucose homeostasis during fasting by gluconeogenesis and formation of ketone bodies. It is also a major site for glycogen storage, glycogenolysis and gluconeogenesis when glycogen stores are depleted.

Lipid metabolism

Fatty acids and lipoproteins are synthesised and the liver is the major site for endogenous cholesterol and prostaglandin production.

Bilirubin metabolism

Haemoglobin is broken down into haem and globin. The globin

Box 1. Detoxification of steroid hormones and drug metabolism

Phase	Reaction
Phase 1	oxidation, reduction, hydrolysis, hydration, dealkylation
Phase 2	glucuronidation, sulphation, acetylation, glutathione conjugation

Formation of Bile: Formation of bile and bile salts by enterohepatic circulation

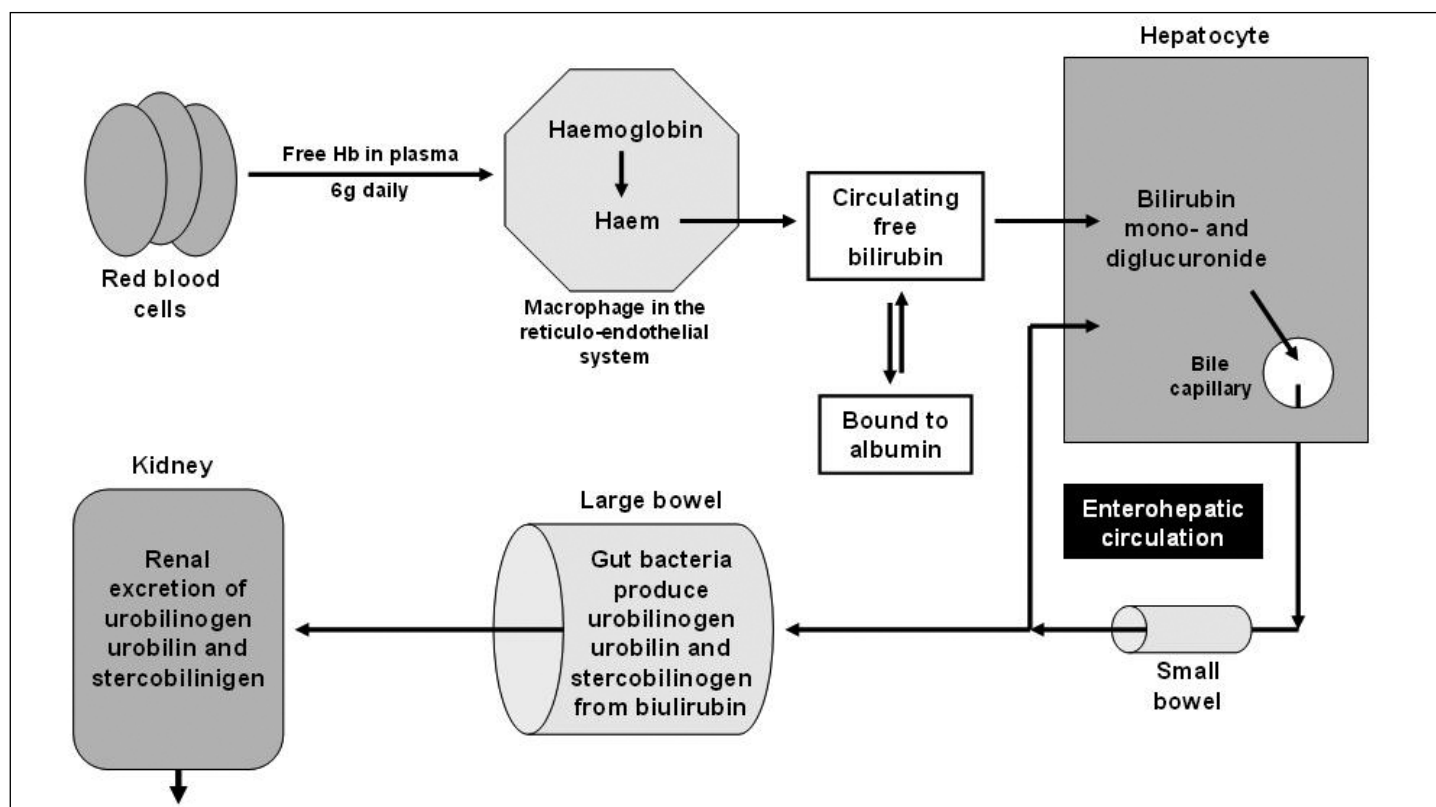


Figure 3. Bilirubin metabolism

Table 2. *Liver function tests*

Test	Relevance
Serum bilirubin	A raised bilirubin is seen clinically as jaundice. Jaundice can be pre-hepatic, hepatocellular and obstructive: <div> <div> Type of jaundice Pre-hepatic Hepatocellular Obstructive </div> <div> Bilirubin elevated Unconjugated Unconjugated or mixed Conjugated </div> </div>
Serum proteins	Impaired synthesis of proteins leading to hypo-proteinaemia and hypo-albuminaemia
Clotting factors	Impaired synthesis leading to raised prothrombin time and INR
Alanine transaminase (ALT) and Aspartate transaminase (AST)	Enzymes released into the circulation by damaged hepatocytes
Alkaline Phosphatase (ALP)	Enzyme localized near bile canaliculi and is raised in biliary obstruction
Other tests	Haemoglobin levels, blood film for evidence of haemolysis, plasma urea and creatinine

part goes into the common amino acid pool. The tetrapyrrole ring of haem opens up to release iron and is converted to biliverdin. Biliverdin is then converted to bilirubin by biliverdin reductase enzyme. This bilirubin remains attached to albumin in the blood as unconjugated or free bilirubin. This then undergoes glucuronidation in the liver to form conjugated bilirubin, which can be excreted in bile. A proportion of the conjugated bilirubin is reabsorbed into the circulation and is excreted by the kidneys as urobilinogen, and some is excreted via the gut as stercobilin and stercobilinogen.

Bile production

The liver produces about one litre of bile per day which passes into the gall bladder and gets concentrated to one fifth of its original volume. Bile consists of electrolytes, proteins, bilirubin, bile salts and lipids. Bile acids are produced in the liver from cholesterol. They are acted upon by bacteria in the gut to form secondary bile acids which are then conjugated to form bile salts. Bile salts are important for emulsification of fat and absorption of the fat soluble vitamins A, D, E and K.

EFFECTS OF ANAESTHESIA ON LIVER FUNCTION

Inhalational anaesthetics affect carbohydrate metabolism in several ways. Ether, unlike the newer agents, enhances the breakdown of glycogen in the liver. Halothane has been shown experimentally, to decrease the rate of glycogenesis, inhibit insulin release and inhibit the effect of insulin on the tissues. The catecholamine mediated stress response to surgery and trauma also increases glycogenolysis, so the overall effect of both surgery and inhalational anaesthesia is to elevate blood glucose. Protein synthesis is reduced by halothane but this is of questionable clinical significance.

Halothane and ether both inhibit the cytochrome p450 enzyme system, slowing the oxidative metabolism of drugs; glucuronide conjugations are not affected. As a result many drugs have a prolonged half-life in the presence of halothane – examples are fentanyl, ketamine, lignocaine, pancuronium and propranolol.

Hepatic blood flow is decreased by halothane in parallel with an overall decrease in cardiac output. Intermittent positive pressure ventilation and decreased PaCO_2 potentiate this effect whilst hypoventilation and increased PaCO_2 results in an increase in hepatic blood flow. These effects are unlikely in isolation to lead to liver hypoxia or damage.

Isoflurane, sevoflurane and desflurane are metabolised by the cytochrome P450 enzyme system and have no deleterious effects on the liver or its metabolism.

Table 3. *Metabolism of volatile agents*

Drug	Liver metabolism (%)
Halothane	25
Isoflurane	0.2
Sevoflurane	3
Desflurane	0.02

Opioids such as morphine, pethidine and fentanyl are known to cause spasm of the Sphincter of Oddi and increase biliary pressure, the effect lasting about two hours in the case of morphine. This should not however preclude their use to provide adequate analgesia in biliary surgery.

Halothane induced hepatic injury

It has been reported that between 1 in 7000 and 1 in 30,000 patients anaesthetised using halothane developed jaundice from severe hepatic damage, after a second halothane anaesthetic. The cause is thought to be multifactorial.

The risk of liver injury due to volatile anaesthetic agents appears to be related to their degree of metabolism with formation of toxic metabolites and an immunological reaction. Coexisting factors, such as reduced hepatic blood flow due to prolonged hypotension and hypoxia, are also partly responsible.

Physiology of Pain

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Summary

Understanding pain physiology is very important in countering it. From what is known it is clear that pain perception involves transduction, transmission, and modulation. Both facilitators and inhibitors are involved. The body response to painful stimuli may be helpful or counter-productive. Better knowledge allows both artificial modulation of pain and suppression of harmful reflex responses

INTRODUCTION

Pain is defined by the International Association for the Study of Pain (IASP) as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage'. Pain has objective, physiological sensory aspects as well as subjective, emotional and psychological components. The term 'nociception' is used only to describe the neural response to traumatic or noxious stimuli.

PERIPHERAL TRANSMISSION

Even though transmission occurs from the peripheral receptor to the brain as one continuous process, for convenience this section is divided into peripheral and central transmission.

Peripheral transmission of pain consists of production of electrical signals at pain nerve endings (transduction) followed by propagation of those signals through the peripheral nervous system (transmission).

Transduction

The primary sensory structure that accomplishes transduction is the nociceptor. Most nociceptors are free nerve endings that sense heat, mechanical and chemical tissue damage. Several types are described:

1. *mechanoreceptors*, which respond to pinch and pinprick,
2. *silent nociceptors* which respond only in the presence of inflammation, and
3. *polymodal mechano-heat nociceptors*. These are most prevalent and respond to excessive pressure, extremes of temperatures ($>42^{\circ}\text{C}$ and $<18^{\circ}\text{C}$), and algogens (pain producing substances). Polymodal nociceptors are slow to adapt to strong pressure and display heat sensitization.

Vanillins are a group of compounds, including capsaicins, that cause pain. An ion channel activated directly by vanilloid compounds including capsaicin (TRPV1, previously known as VR1) has been found to

be selectively overexpressed in some small to medium diameter nociceptive neurons.¹ The TRPV1 receptors not only respond to pain but also to protons and to temperatures $>43^{\circ}\text{C}$. There are multiple TRPV1 splice variants.¹

Transmission

Pain impulses are transmitted by two fibre systems. The presence of two pain pathways explains the existence of two components of pain: fast, sharp and well localized sensation ('first' pain) which is conducted by A δ fibres, while a duller slower onset and often poorly localized sensation ('second pain') is conducted by C fibres. A δ fibres are myelinated, 2-5mcm in diameter and conduct at rates of 12 to 30m.s⁻¹, whereas C fibres are unmyelinated, 0.4-1.2mcm in diameter and conduct at rates of 0.5 to 2m.s⁻¹. Both fibre groups end in the dorsal horn of the spinal cord. A δ fibres predominantly terminate on neurons in lamina I of the dorsal horn, whereas the dorsal root C fibres terminate in laminae II and III. The synaptic junctions between these first order neurons and the dorsal horn cells in the spinal cord are sites of considerable plasticity (i.e. the synaptic connections demonstrate the ability to change the strength of their relationship). For this reason the dorsal horn has been called a gate, where pain impulses can be modified (or 'gated').

Second-order neurons are either nociceptive-specific or wide dynamic range (WDR) neurons. Nociceptive-specific neurons serve only noxious stimuli and are arranged somatotopically in lamina I of the dorsal horn of the spinal cord. This means that they have a discrete somatic receptive field and are spatially arranged in the central nervous system according to the part of the body that they innervate. They are normally silent and respond only to high threshold noxious stimuli. WDR neurons receive both noxious and non-noxious afferent input from A β , A δ and C fibres. Differentiation between noxious and innocuous stimuli occurs by a higher frequency of WDR neuron discharge to noxious stimuli. WDR neurons are most abundant in lamina V.

CENTRAL TRANSMISSION

Central transmission includes transmission and

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perception whereby the electrical signals are transmitted from the spinal cord to the brain.

Transmission

The axons of most of the second order neurons cross the midline at the anterior commissure to the contralateral side of the spinal cord, and ascend as the spinothalamic tract. This tract ends in the thalamus, reticular formation, nucleus raphe magnus and the periaqueductal grey and can be divided into lateral and medial parts. The lateral spinothalamic (neospinothalamic) tract projects mainly to the ventral posterolateral nucleus of the thalamus and carries discriminative aspects of pain, such as location, intensity, and duration of pain. The medial spinothalamic (paleospinothalamic) tract projects to the medial thalamus and is responsible for mediating the autonomic and unpleasant emotional perception of pain.

Perception

The third order neurons project from the thalamus to somatosensory areas I and II in the post-central gyrus and superior wall of the sylvian fissure. Perception and discrete localization of pain take place in these cortical areas. Some fibres project to the anterior cingulate gyrus and are likely to mediate the suffering and emotional components of pain.

MODULATION

Modulation of pain occurs peripherally at the nociceptor, in the spinal cord, or in supraspinal structures. This modulation can either inhibit or facilitate pain.

Peripheral modulation

Nociceptors and their neurons display sensitization following repeated stimulation. Sensitization of nociceptors results in a decrease in threshold, an increase in frequency response, a decrease in response latency and spontaneous firing, even after cessation of the stimulus ('after discharges'). This primary hyperalgesia (increased sensitivity to pain) is mediated by release of algogens like histamine, bradykinin, PGE₂ and leukotrienes from damaged tissues.

Secondary hyperalgesia or neurogenic inflammation is manifested by the triple response of flare, local oedema and sensitization to noxious stimuli. It is primarily due to antidromic release of substance P from collateral axons of primary afferent neurons. Substance P degranulates histamine and serotonin, vasodilates blood vessels, causes tissue oedema and induces formation of leukotrienes.

Central modulation

Modulation can either facilitate or inhibit pain. The mechanisms for facilitation are:

1. Windup and sensitization of second order neurons
2. Receptive field expansion
3. Hyperexcitability of flexion responses.

Neurochemical mediators of central sensitization include substance P, CGRP (calcitonin gene related peptide), VIP (vasointestinal peptide), cholecystokinin, angiotensin, galanin, L-glutamate and L-aspartate. These substances trigger changes in membrane excitability by

interacting with G-protein coupled receptors, activating intracellular second messengers, which in turn phosphorylate substrate proteins. A common pathway leads to increased intracellular calcium concentration. For example glutamate and aspartate activate the NMDA receptor. Stimulation of ionotropic NMDA receptors causes intraneuronal elevation of Ca²⁺, which stimulates nitric oxide synthase (NOS) and the production of nitric oxide (NO). NO as a gaseous molecule diffuses out from the neuron and by action on guanylyl cyclase, NO stimulates the formation of cGMP in neighbouring neurons. Depending on the expression of cGMP-controlled ion channels in target neurons, NO may be excitatory or inhibitory. NO has been implicated in the development of hyperexcitability, resulting in hyperalgesia or allodynia (a painful response to a usually non-painful stimulus), by increasing nociceptive transmitters at their central terminals.

Inhibitory mechanisms

Inhibitory mechanisms can be either segmental or supraspinal.

Segmental inhibition consists of activation of large afferent fibres subserving epicritic sensation, inhibitory WDR neurones and spinothalamic activity. Glycine and γ-amino butyric acid (GABA) are amino acids that function as inhibitory neurotransmitters. Segmental inhibition appears to be mediated by GABA-B receptor activity, which increases K⁺ conductance across the cell membrane.

Supraspinal inhibition occurs whereby several supraspinal structures send fibres down the spinal cord to inhibit pain at the level of the dorsal horn. These include periaqueductal grey, reticular formation, and nucleus raphe magnus (NRM). Axons from these structures act pre-synaptically on the primary afferent neurons and post-synaptically on second-order neurons (or interneurons). These inhibitory pathways utilise monoamines, such as norepinephrine and serotonin, as neurotransmitters and terminate on nociceptive neurons in the spinal cord as well as on spinal inhibitory interneurons which store and release opioids. Norepinephrine mediates this action through α₂ receptors. The endogenous opiate system act via enkephalins and β-endorphins. These mainly act presynaptically whereas the exogenous opiates act postsynaptically.

REFLEX RESPONSES

Somatic and visceral pain fibres are fully integrated with the skeletal motor and sympathetic systems in the spinal cord, brain stem and higher centers. These synapses are responsible for reflex muscle activity that is associated with pain. In a similar fashion reflex sympathetic activation causes the release of catecholamines, locally and from the adrenal medulla. This increases heart rate and blood pressure with a consequent increase in myocardial work, increased metabolic rate and oxygen consumption. Gastrointestinal tone is decreased leading to delayed gastric emptying.

Pain also causes an increase in the secretion of catabolic hormones and decreased secretion of anabolic hormones. The metabolic responses to pain include hyperglycaemia due to gluconeogenesis and decreases in insulin secretion or action increased protein metabolism and increased lipolysis. The respiratory responses could be either hyperventilation due to stimulation of respiratory center or hypoventilation due to splinting and reflex muscle spasm. The diencephalic and cortical

responses may include anxiety and fear. Pain stimulates psychological mechanisms with deleterious emotional effects.

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Physiological Changes Associated with Pregnancy

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CARDIOVASCULAR SYSTEM

The pregnancy induced changes in the cardiovascular system develop primarily to meet the increased metabolic demands of the mother and fetus.

Blood volume

Blood volume increases progressively from 6-8 weeks gestation (pregnancy) and reaches a maximum at approximately 32-34 weeks with little change thereafter. Most of the added volume of blood is accounted for by an increased capacity of the uterine, breast, renal, striated muscle and cutaneous vascular systems, with no evidence of circulatory overload in the healthy pregnant woman. The increase in plasma volume (40-50%) is relatively greater than that of red cell mass (20-30%) resulting in haemodilution and a decrease in haemoglobin concentration. Intake of supplemental iron and folic acid is necessary to restore haemoglobin levels to normal (12g.dl^{-1}). The increased blood volume serves two purposes. First, it facilitates maternal and fetal exchanges of respiratory gases, nutrients and metabolites. Second, it reduces the impact of maternal blood loss at delivery. Typical losses of 300-500ml for vaginal births and 750-1000ml for caesarean sections are thus compensated with the so-called 'autotransfusion' of blood from the contracting uterus.

Blood constituents

As mentioned above, red cell mass is increased 20-30%. Leukocyte counts are variable during gestation, but usually remain within the upper limits of normal. Marked elevations, however, develop during and after parturition (delivery). Fibrinogen, as well as total body and plasma levels of factors VII, V11, IX, and X increase markedly. The number of platelets also rises, yet not above the upper limits of normal and this is combined with a decrease in fibrinolytic activity. All these changes tend to make pregnancy a relatively hypercoagulable state. This prevents excessive bleeding at delivery but increases the risk of thrombo-embolic complications. At delivery there is an increase in fibrinolytic activity, especially the third stage, and a high concentration of plasminogen activators in the uterus, both of which may activate disseminated intravascular coagulopathy.

Cardiac output

Cardiac output increases to a similar degree as the blood volume. During the first trimester cardiac output is 30-40% higher than in the non-pregnant state. Steady rises are shown on Doppler echocardiography, from an average of 6.7l.min^{-1} at 8-11 weeks to about 8.7l.min^{-1} flow at 36-39 weeks; they are due, primarily, to an increase in stroke volume (35%) and, to a lesser extent, to a more rapid heart rate (15%). There is a steady reduction in systemic vascular resistance (SVR) which contributes towards the hyperdynamic circulation observed in pregnancy.

During labour further increases are seen with pain in response to increased catecholamine secretion; this increase can be blunted with the institution of labour analgesia. Also during labour, there is an increase in intravascular volume by 300-500ml of blood from the contracting uterus to the venous system.

Following delivery this autotransfusion compensates for the blood losses and tends to further increase cardiac output by 50% of pre-delivery values. At this point, stroke volume is increased while heart rate is slowed. The left ventricular work of the heart is increased by 40%. This represents a high risk period for parturients with cardiac disease.

Cardiac size, position and the ECG

There are both size and position changes which can lead to changes in ECG appearance. The heart is enlarged by both chamber dilation and hypertrophy. Dilation across the tricuspid valve can initiate mild regurgitant flow causing a normal grade I or II systolic murmur. Upward displacement of the diaphragm by the enlarging uterus causes the heart to shift to the left and anteriorly, so that the apex beat is moved outward and upward. These changes lead to common ECG findings of left axis deviation, sagging ST segments and frequently inversion or flattening of the T wave in lead III.

Blood pressure

Systemic arterial pressure is never increased during normal gestation. In fact, by mid-pregnancy, a slight decrease in diastolic pressure can be recognized. Pulmonary arterial pressure also maintains a constant

Summary

Physiological and anatomical alterations develop in many organ systems during the course of pregnancy and delivery. Early changes are due, in part, to the metabolic demands brought on by the fetus, placenta and uterus and to the increasing levels of pregnancy hormones. Later changes, starting in mid-pregnancy, are anatomical in nature and are caused by mechanical pressure from the expanding uterus. These alterations create unique requirements for the anaesthetic management of the pregnant woman.

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level. However, vascular tone is more dependent upon sympathetic control than in the non-pregnant state, so that hypotension develops more readily and more markedly consequent to sympathetic blockade following spinal or extradural (epidural) anaesthesia. Central venous and brachial venous pressures remain unchanged during pregnancy, but femoral venous pressure is progressively increased due to mechanical factors. There is also a reduction in afterload and an increase in preload which, together with the increase in blood volume, may produce functional murmurs.

Aorto-caval compression

From mid-pregnancy, the enlarged uterus compresses both the inferior vena cava and the lower aorta when the patient lies supine. Obstruction of the inferior vena cava reduces venous return to the heart leading to a fall in cardiac output by as much as 24% towards term. This occurs with all women in the third trimester in the supine position to some extent. This can be concealed, such as in the unanaesthetised state when most women are capable of compensating for the resultant decrease in stroke volume by increasing systemic vascular resistance and heart rate, or revealed during anaesthesia when these compensatory mechanisms are reduced or abolished so that significant hypotension may rapidly develop.

The main consequence of aorto-caval compression is a reduction in venous return and subsequently cardiac output and blood pressure. As well as leading to maternal hypoxia it also causes impaired uteroplacental flow which leads to fetal hypoxia and acidosis. Obstruction of the lower aorta and its branches also causes diminished blood flow to kidneys, and lower extremities. During the last trimester, maternal renal function is markedly lower in the supine than in the lateral position. There are alternative venous pathways (the paravertebral and azygos systems), through which venous return is diverted.

Venous distension

Venous caliber increases to approximately 150% during the course of gestation and the venous ends of capillaries become dilated, causing reduced blood flow. These vascular changes contribute to delayed absorption of subcutaneously or intramuscularly injected substances. Distension of the extradural veins heightens the risk of vascular damage during institution of a regional block. The increased venous volume within the rigid spinal canal reduces the volume or capacity of the extradural and intrathecal spaces for local anaesthetic solutions. This will therefore increase the spread of injected drugs. During labour, venous pressure increases by 4–6cmH₂O in the first stage and by up to 50cmH₂O in the second stage during contractions.

Clinical implications

Despite the increased workload of the heart during gestation and labour, the healthy woman has no impairment of cardiac reserve. In contrast, for the gravida with heart disease and low cardiac reserve, the increase in the work of the heart may cause ventricular failure and pulmonary oedema. In these women, further increases in cardiac workload during labour must be prevented by effective pain relief, optimally provided by extradural or spinal analgesia. Since cardiac output is highest in the immediate postpartum period, sympathetic blockade should be maintained for several hours after delivery and then weaned off slowly.

Teaching point

There is a 30% reduction in volume of local anaesthetic solution required at term when compared to the non-pregnant woman, to achieve the same block.

Aorto-caval compression and its sequelae must be avoided. No woman in late pregnancy should lie supine without manipulating the uterus off the great abdomino-pelvic vessels. During labour, the parturient should rest on her side, left or right.

During Caesarean section and for other indications demanding the supine position, the uterus should be displaced, usually to the left, by placing a rigid wedge under the right hip and/or tilting the table left side down.

RESPIRATORY SYSTEM

Changes within the respiratory system are of great significance to the anaesthetist.

Respiratory tract

Hormonal changes to the mucosal vasculature of the respiratory tract lead to capillary engorgement and swelling of the lining in the nose, oropharynx, larynx, and trachea. Symptoms of nasal congestion, voice change and upper respiratory tract infection may prevail throughout gestation. These symptoms can be exacerbated by fluid overload or oedema associated with pregnancy-induced hypertension (PIH) or pre-eclampsia. In such cases, manipulation of the airway can result in profuse bleeding from the nose or oropharynx. Endotracheal intubation can be difficult and a smaller than usual endotracheal tube may be required to fit through the larynx. Airway resistance is reduced, probably due to the progesterone-mediated relaxation of the bronchial musculature.

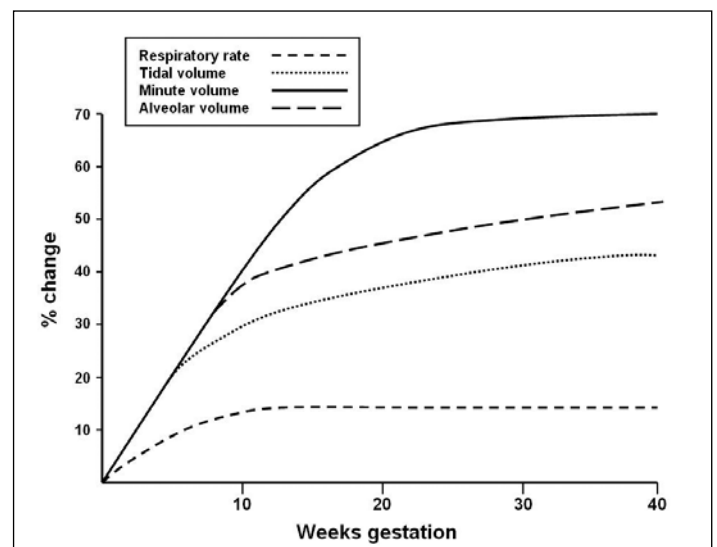


Figure 1. Respiratory changes in pregnancy

Lung volumes

Upward displacement by the gravid uterus causes a 4cm elevation of the diaphragm, but total lung capacity decreases only slightly because of compensatory increases in the transverse and antero-posterior diameters of the chest by as much as 5–7cm, as well as flaring of the ribs. These changes are brought about by hormonal

effects that loosen ligaments. Despite the upward displacement, the diaphragm moves with greater excursions during breathing in the pregnant than in the non-pregnant state. In fact, breathing is more diaphragmatic than thoracic during gestation, an advantage during supine positioning and high regional blockade.

From the middle of the second trimester, expiratory reserve volume, residual volume and functional residual volume are progressively decreased, by approximately 20% at term. Lung compliance is relatively unaffected, but chest wall compliance is reduced, especially in the lithotomy position.

Ventilation and respiratory gases

A progressive increase in minute ventilation starts soon after conception and peaks at 50% above normal levels around the second trimester. This increase is effected by a 40% rise in tidal volume and a 15% rise in respiratory rate ($2\text{--}3\text{ breaths}\cdot\text{min}^{-1}$). Since deadspace remains unchanged, alveolar ventilation is about 70% higher at the end of gestation. Arterial and alveolar carbon dioxide tensions are decreased by the increased ventilation. An average PaCO_2 of 4.3kPa (32mmHg) and arterial oxygen tension of 13.7kPa (105mmHg) persist during most of gestation. The development of alkalosis is forestalled by compensatory decreases in serum bicarbonate. Only carbon dioxide tensions below 3.7kPa (28mmHg) lead to a respiratory alkalosis.

During labour ventilation may be further accentuated, either voluntarily (Lamaze method of pain control and relaxation) or involuntarily in response to pain and anxiety. Such excessive hyperventilation results in marked hypocarbia and severe alkalosis, which can lead to cerebral and uteroplacental vasoconstriction and a left shift of the oxygen dissociation curve. This reduces the release of oxygen from haemoglobin, with consequent decreased maternal tissue oxygenation as well as reduced oxygen transfer to the fetus. Furthermore, episodes of hyperventilation may be followed by periods of hypoventilation as the blood carbon dioxide tension (PaCO_2) returns to normal. This may lead to both maternal and fetal hypoxia.

Oxygen consumption increases gradually in response to the needs of the growing fetus, culminating in a rise of at least 20% at term. During labour, oxygen consumption is further increased (up to and over 60%) as a result of the exaggerated cardiac and respiratory work load. This remains high after delivery to pay off the oxygen debt and correct the levels.

Clinical implications

The changes in respiratory function have clinical relevance for the anaesthesiologist. General anaesthesia is not the routine choice of anaesthetic for caesarian section because of the airway problems associated with pregnancy. These problems result from anatomical changes such as enlarged breasts and oedema of the airway, that make intubation more difficult. The failed intubation rate increases to 1 in 250 and is worse in the obese and those suffering from pre-eclampsia. There is also an increased risk of aspiration because of the gastrointestinal changes, and, most importantly, the increased oxygen consumption and the decreased reserve due to the reduced functional residual capacity, can result in a rapid fall in arterial oxygen tension

during apnoea. This occurs despite careful maternal positioning and preoxygenation. The increased minute ventilation combined with decreased functional residual capacity hastens inhalation induction or changes in depth of anaesthesia when breathing spontaneously.

GASTROINTESTINAL SYSTEM

Since aspiration of gastric contents is an important cause of maternal morbidity and mortality in association with anaesthesia, an examination of the controversy surrounding gastrointestinal changes in pregnancy is justified. The intragastric pressure is normally 7-8cmH₂O, this increases to 13-17cmH₂O in pregnancy and can increase to 40cmH₂O with twins and in the obese.

Mechanical changes

The enlarging uterus causes a gradual cephalad displacement of stomach and intestines. At term the stomach has attained a vertical position rather than its normal horizontal one. These mechanical forces lead to increased intragastric pressures as well as a change in the angle of the gastroesophageal junction, which in turn tends toward greater oesophageal reflux.

Physiological changes

The hormonal effects on the gastrointestinal tract are an issue of debate among anaesthetists. Relaxation of the lower oesophageal sphincter has been described, but there have been differing views about the effect on motility of the gastrointestinal tract and the times at which it is most prominent. Many believe that there is also retardation of gastrointestinal motility and gastric emptying, producing increased gastric volume with decreased pH, beginning as early as 8-10 weeks of gestation. Recent studies, however, have shed a different light on the subject. Measuring peak plasma concentrations of drugs absorbed exclusively in the duodenum in both non-pregnant and pregnant volunteers, at different times of gestation, it was shown that peak absorption occurred at the same interval in all women with the exception those in labour. This suggests that gastric emptying is delayed only at the time of delivery.

Thus, the raised risk of aspiration is due to an increase of oesophageal reflux and decreased pH of gastric contents. The heightened incidence of difficult endotracheal intubations worsens the situation.

Teaching point

The pregnant woman should be considered to be a 'full stomach' patient with increased risk of aspiration during most of gestation.

Pulmonary aspiration of gastric contents can occur either following vomiting (active) or regurgitation (passive). Aspiration of solid material causes atelectasis, obstructive pneumonitis or lung abscess, while aspiration of acidic gastric contents results in chemical pneumonitis (Mendelson's syndrome). The most serious consequences follow aspiration of acidic materials containing particulate matter as may follow swallowing certain antacids such as magnesium trisilicate. Clear antacids such as sodium citrate (0.3mol) or bicarbonate should be used. While the incidence of pulmonary aspiration of solid food has decreased due to patient education, that of gastric acid has remained constant.

Clinical implications

The danger of aspiration is almost eliminated when regional anaesthesia or inhalational analgesia is used. During general anaesthesia airway protection by means of a cuffed endotracheal tube is mandatory. Although awake intubation is safest, discomfort and the lack of patient cooperation and discomfort prevent it being the routine method for securing the airway. The endotracheal tube is placed immediately following loss of consciousness after induction of general anaesthesia.

Teaching point

Special precautions should be heeded, even when induction to intubation time is expected to be brief, to prevent the regurgitation:

1. Supine position with lateral tilt to minimise any increase in intragastric pressure.
2. Preoxygenation prior to induction then no positive pressure ventilation prior to insertion of the endotracheal tube to prevent distention of the stomach with gas (rapid sequence induction).
3. Cricoid pressure (Sellick's manoeuvre) during induction which is maintained until endotracheal tube placement in the trachea has been confirmed. Cricoid pressure should be applied to the cricoid cartilage whilst supporting the back of the neck. This occludes the oesophagus, thus obstructing the path of regurgitation.

The acidity and volume of gastric contents can be reduced by pharmacologic interventions which may prove invaluable. Most importantly, a nonparticulate oral antacid, 30ml of sodium 0.3molar citrate or bicarbonate, should be given immediately prior to induction of general anaesthesia to all women. In addition, histamine H₂-receptor antagonist the night before and the morning of delivery may reduce secretion of hydrochloric acid (ranitidine 150mg orally).

METABOLISM

All metabolic functions are increased during pregnancy to provide for the demands of fetus, placenta and uterus as well as for the gravida's increased basal metabolic rate and oxygen consumption. Protein metabolism is enhanced to supply substrate for maternal and fetal growth. Fat metabolism increases as evidenced by elevation in all lipid fractions in the blood. Carbohydrate metabolism, however, demonstrates the most dramatic changes. Hormones such as human placental lactogen, progesterone, prolactin and cortisol, together with reduced liver enzyme activity of glucokinase and phosphofructokinase, result in an insulin resistant state. Normal women counteract this by increasing their production of insulin, however women with gestational diabetes are unable to do this. As early as 15 weeks of gestation, maternal blood glucose levels after an overnight fast are considerably lower than in the nongravid state, this is due to altered hormonal balance, expanded maternal blood volume, increased placental transfer of glucose and loss through the kidneys because of a low renal threshold.

RENAL PHYSIOLOGY

Renal plasma flow and glomerular filtration rate begin to increase progressively during the first trimester. At term, both are 50-60%

higher than in the non-pregnant state. This parallels the increases in blood volume and cardiac output. The elevations in plasma flow and glomerular filtration result in an elevation in creatinine clearance. Blood urea and serum creatinine are reduced by 40%. The increase in glomerular filtration may overwhelm the ability of the renal tubules to reabsorb leading to glucose and protein losses in the urine. Thus, mild glycosuria (1-10g.day⁻¹) and/or proteinuria (to 300mg.day⁻¹) can occur in normal pregnancy. There is also an increase in filtered sodium, but tubular absorption is increased by an increase in aldosterone secretion, via the renin-angiotensin mechanism. There is also a decrease in plasma osmolality. This is a measure of the osmotic activity of a substance in solution and is defined as the number of osmoles in a kilogram of solvent. In practice it indicates that the plasma concentrations of electrolytes, glucose and urea fall if, for example, more water than sodium is retained. Over the whole period of gestation there is retention of 7.5l of water and 900mmol of sodium.

After the 12th week of gestation, progesterone can induce dilation and atony of the renal calyces and ureters. With advancing gestation, the enlarging uterus can compress the ureters as they cross the pelvic brim and cause further dilatation by obstructing flow. These changes may contribute to the frequency of urinary tract infections during pregnancy. The effect of postural compression of the aortic branches perfusing the kidneys has been discussed.

DRUG RESPONSES

The response to anaesthetic and adjuvant drugs is modified during pregnancy and the early puerperium. The most pertinent alteration is a reduced drug requirement, manifest in both regional and general anaesthesia.

Regional anaesthesia

From the late first trimester to the early puerperium, a smaller dose of local anaesthetic is required to obtain the desired level of spinal or extradural blockade. During the last months of gestation, approximately two-thirds of the normal dose is adequate. This altered response, which is due to CSF and hormonal changes and an increase in volume of the epidural veins, subsides progressively in the early postpartum period.

General anaesthesia

Induction and changes in depth of inhalation anaesthesia occur with greater rapidity in pregnant women than in non-pregnant subjects. Pregnancy enhances anaesthetic uptake in two ways. The increase in resting ventilation delivers more agent into the alveoli per unit time, while the reduction in functional residual capacity favors rapid replacement of lung gas with the inspired agent. In addition, there is a reduction in anaesthetic requirements, with a fall in the minimum alveolar concentrations (MAC) of halogenated vapors. When measured in sheep MAC was 25-40% lower in gravid as compared with non-pregnant animals.

The decreased functional residual capacity has a further effect on the management of general anaesthesia. As referred to earlier, the resultant reduction in oxygen storage capacity, together with the elevated oxygen consumption, leads to an unusually rapid decline in arterial oxygen tension in the apnoeic anaesthetised gravida.

There are also alterations in the response to intravenous agents, in particular prolongation of their elimination half-lives consequent to the greater distribution volume (resulting from the pregnancy-induced increase in plasma volume). Thus, the mean elimination half-life for thiopentone in gravid women is more than doubled in comparison with that in non-gravid young patients.

Serum cholinesterase. Serum cholinesterase levels fall by 24-28% during the first trimester without a marked change for the remainder of gestation. However, even lower levels (about 33% reduction) develop during the first seven postpartum days. The decreased levels of the enzyme are still sufficient for normal hydrolysis of clinical doses of suxamethonium or chloroprocaine during gestation. Postpartum, however, approximately 10% of women will be at risk of a prolonged reaction to suxamethonium.

Clinical implications

These altered drug responses must be taken into consideration whenever a patient is pregnant or in the early puerperium.

CONCLUSION

A good understanding of the physiological changes in pregnancy is essential in the management of both the well woman, but also in those women who have a pre-existing medical condition. Anticipation of these problems should be part of routine ante-natal care and referral to a tertiary centre should be made if it is felt serious. This has been highlighted in *Saving Mother's Lives*, the UK's triannual report into maternal morbidity and mortality 2003-2005 (available at www.cemach.org.uk).

PHARMACOLOGY

- 80 An Introduction to Pharmacology and Drug Doses**
Lauren Barker
- 82 Pharmacokinetics and Anaesthesia**
Fred Roberts and Dan Freshwater-Turner
- 86 Pharmacodynamics and Receptor Physiology**
James Noblet
- 90 The Pharmacology of the Autonomic Nervous System**
Oliver Pratt and Carl Gwinnutt
- 96 Intravenous Drugs used for the Induction of Anaesthesia**
Tom Lupton and Oliver Pratt
- 102 Pharmacology of Inhalational Anaesthetics**
John Myatt
- 108 Pharmacology of Neuromuscular Blocking Drugs and Anticholinesterases**
Dominic O'Connor and Carl Gwinnutt
- 112 Paracetamol - A Review of Three Routes of Administration**
Chris Oscier, Nicki Bosley and Quentin Milner
- 115 Non-steroidal Anti-inflammatory Drugs**
Ben Gupta
- 118 Pharmacology of Opioids**
Mahesh Trivedi, Shafee Shaikh and Carl Gwinnutt
- 125 Local Anaesthetic Pharmacology**
Hiliary Edgcombe and Graham Hocking

An Introduction to Pharmacology and Drug Doses

Lauren Barker

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DOSES OF DRUGS IN ANAESTHESIA

Drugs in anaesthesia are commonly expressed in grams, milligrams or micrograms which refer to their mass.

Abbreviations are often used:

Mass	Abbreviation
kilogram	kg
gram	g
milligram	mg
microgram	mcg
nanogram	ng

Examples:

1g flucloxacillin, 500mg thiopentone, 600mcg atropine. The words milli-, micro- and nano- which appear in front of “gram” refer to how many multiples of 10 are present.

- It is possible to convert from grams to nanograms as follows:

$$1\text{g} = 1\,000\text{mg} = 1\,000\,000\text{mcg} = 1\,000\,000\,000\text{ng}$$

- To convert, for example, from micrograms to milligrams:

$$600\text{mcg atropine} = 0.6\text{mg atropine}$$

RECOMMENDED OR THERAPEUTIC DRUG DOSES

Recommended or therapeutic doses enable one to calculate the correct dose of drug for the patient undergoing anaesthesia. These doses were previously expressed as mg/kg or mcg/kg but should now formally be written as mg.kg⁻¹ or mcg.kg⁻¹ and are calculated as follows:

Example:

The dose of atropine is 20mcg.kg⁻¹

- To calculate the correct dose of drug for a patient, multiply the drug dose by the patient's weight. In a 20kg patient we would give:

$$\begin{aligned}20\text{mcg.kg}^{-1} &= 20\text{mcg.kg}^{-1} \times 20\text{kg} = \\ &400\text{mcg} = 0.4\text{mg}\end{aligned}$$

- To calculate the correct dose of atracurium (0.5mg.kg⁻¹) for a 70kg adult.

$$0.5\text{mg.kg}^{-1} \times 70\text{kg} = 35\text{mg}$$

MAXIMUM DOSES

Maximum doses may refer to local anaesthetic drugs like lignocaine or bupivacaine and indicate the maximum dose of drug that may be given to the patient safely without causing toxicity. In the case of local anaesthetics cardiac arrhythmias or convulsions may result if the maximum dose is exceeded.

OTHER UNITS FOR DESCRIBING DRUGS

Most commonly we describe the amount of drug present by reference to the mass of drug (see above). However drug preparations may also be described by how many particles they contain. This gives an idea of the amount of drug present rather than the mass of the drug.

By convention the amount of a substance is measured in moles (abbreviation: mol). A mole has been defined by the Système International as the quantity of a substance that contains the same number of particles as there are atoms in 12g of carbon-12. There are 6.022×10^{23} atoms present in 12g carbon-12 and this equals one mole. (6.022×10^{23} is the abbreviated way of writing a large number – written in full you would have to move the decimal point to the right 23 times i.e. 6022 followed by 20 zero's).

This dose method is often used for substances such as potassium (K⁺) or sodium (Na⁺) in the form of millimole (1mole = 1000 millimole - often written as mmol). This method is useful as sodium or potassium are often prepared with chloride and when administered it is helpful to consider only the amount of Na⁺ or K⁺ that is given. Therefore it is usually described in mmol.

Example:

A solution of normal saline contains 154mmol Na⁺ and 154mmol Cl⁻ in each litre.

Summary

This article explains the internationally recognised formats for describing drugs, their dosage and dilutions. Commonly encountered dilutions of drugs such as epinephrine (adrenaline) and local anaesthetic agents are clarified using examples. The recommended international non-proprietary names (rINN) of some of the more commonly encountered anaesthetic and critical care drugs are listed.

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DRUGS IN CONCENTRATIONS

When a substance is dissolved in a liquid it forms a solution. The volume of a solution is expressed in litres or millilitres. 1litre = 1000ml.

The substance dissolved is known as the solute. The amount of solute in a solution is expressed as a concentration. The amount of solute may be described by its mass (grams or milligrams per litre) or by its amount (moles per litre or millimoles per litre).

If the solute has a known chemical formula (e.g. salt - NaCl), then it is preferable to use mol.l⁻¹ or mmol.l⁻¹. If the solute does not have a defined chemical composition (such as a protein), then mg.l⁻¹ or g.l⁻¹ is used.

Some solutions such as local anaesthetics and thiopentone that are used in anaesthesia on a daily basis are expressed as a percentage e.g. lignocaine 2% and thiopentone 2.5%.

When using drugs prepared in this way it is necessary to calculate the number of mg in ml of solution. This is easiest done by multiplying the percentage of the solution by 10:

- 2% lignocaine x 10 = 20mg.ml⁻¹
- 0.5% bupivacaine x 10 = 5mg.ml⁻¹
- 2.5% thiopentone x 10 = 25 mg.ml⁻¹

The maths behind this calculation is as follows:

- A 2.5% solution means that there is 2.5g of thiopentone in 100ml:

$$\begin{aligned} & 2.5\text{g in } 100\text{ml} \\ & = 2500\text{mg in } 100\text{ml} \\ & = 25\text{mg in } 1\text{ml (} 25\text{mg.ml}^{-1}\text{)} \end{aligned}$$

Some solutions such as epinephrine (adrenaline) may be expressed as 1:1000 or 1:10 000 or 1:100 000. This means that in a 1:1000 epinephrine ampoule there is one part epinephrine to 1000 parts solution.

To work out how many milligrams of epinephrine are present:

- 1:1000 solution epinephrine
 - = 1g epinephrine in 1000ml solution
 - = 1000mg epinephrine per 1000ml solution
 - = 1mg per ml
- 1:10 000 solution epinephrine
 - = 1g epinephrine in 10,000ml solution
 - = 1000mg per 10,000ml
 - = 1mg per 10ml which can also be expressed as 100mcg per ml

PREPARING LOCAL ANAESTHETICS WITH EPINEPHRINE

Pre-mixed ampoules of lignocaine 1% and 2% with adrenaline are sometimes not available and it may be necessary to prepare these solutions locally. A 1:200 000 solution means that there is 1 part adrenaline to 200 000 parts of solution (lignocaine in this instance).

In order to produce a 1:200 000 adrenaline solution, add 0.1ml adrenaline 1:1000 to 20ml lignocaine. The method is as follows:

- Take 1ml of adrenaline 1:1000 - dilute to 10mls with saline.
- Take 1ml of this mix which is now 1ml of 1:10 000 adrenaline. Add 19ml lignocaine.
- Total solution is now 20mls and the original adrenaline has been diluted 200 times = 1:200 000 solution

OTHER UNITS - MILLIEQUIVALENTS (mEq)

Sometimes the term milliequivalent is used in textbooks, although millimoles is the more correct expression. When substances are dissolved in a liquid, they may develop a charge. For example, when salt (NaCl) is dissolved in water, it separates into its two components: Na⁺ and Cl⁻ (these are known as ions). Sodium ions have one positive charge and chloride ions have one negative charge. The word milliequivalent refers to how many ions are present. In this case the number of milliequivalents will be the same as the number of millimoles in solution.

Example:

A plasma sodium concentration of 140mEq.l⁻¹ equals 140mmol.l⁻¹.

However, in a magnesium chloride solution (MgCl₂) the magnesium ion has two positive charges (Mg²⁺) so there will be two milliequivalents of magnesium per litre of solution. In this case the number of milliequivalents will not equal the number of millimoles.

CHANGES IN DRUG NAMES

New regulations from the EEC now require the use of the Recommended International Non-proprietary Name (rINN) for drugs. In drugs where there is concern that a name change may pose a serious risk to patients, both the British Approved Name (BAN) and the rINN name will appear on the drug ampoule for at least the next 5 years. In other cases, the new name will appear alone.

Some examples of name changes that will affect anaesthetists are:

UK name	rINN name
adrenaline	epinephrine
noradrenaline	norepinephrine
frusemide	furosemide
lignocaine	lidocaine
thiopentone	thiopental
phenobarbitone	phenobarbital

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Pharmokinetics and Anaesthesia

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INTRODUCTION

Pharmacokinetics explains what happens to a drug in the body, whereas pharmacodynamics describes the actions produced by the drug on the body. Therefore, the effects of a drug result from a combination of its pharmacokinetic and pharmacodynamic characteristics in that individual. Wherever possible, drug administration should be based on a measured patient response, which will incorporate both of these aspects of its pharmacology. However, such an approach may not always be possible. The response may be masked by other factors (e.g. neuromuscular blockers masking signs of anaesthetic depth) or difficult to quantify precisely (e.g. action of antibiotics or anti-emetics). Under these circumstances, previously established pharmacokinetic and pharmacodynamic data are used to guide administration. This article aims to explain and simplify the principles of pharmacokinetics so that their application to clinical practice can be better understood.

GENERAL PRINCIPLES

Membrane transfer

Drugs need to cross cell membranes in order to produce their effects (e.g. gastro-intestinal absorption, reaching intracellular sites of action). Such transfer occurs more readily with a:

- low degree of ionization
- low molecular weight
- high lipid solubility
- high concentration gradient.

The extent of ionization is influenced substantially by environmental pH, an effect that is used to prepare highly ionized, aqueous solutions of acidic drugs such as thiopental (solution pH 10.5) or basic ones such as lidocaine (solution pH 5.2), as shown in Figure 1. In the more neutral pH of the body, much of the drug reverts to the unionized form enabling membrane transfer to reach its site of action. If this change in pH does not occur, the drug cannot become unionized and will be ineffective (e.g. lidocaine in the acidic environment of infected tissue).

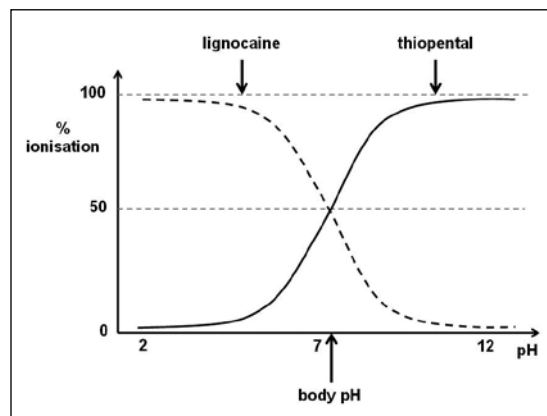


Figure 1. Ionization and environmental pH. Arrows indicate the pH at which lidocaine (a weak base) and thiopental (a weak acid) are prepared in solution. At body pH, much of the drug becomes unionized and can cross membranes

Partial pressure and solubility

For an inhaled drug, it is the partial pressure that largely determines its behaviour, both for moving between phases and producing pharmacodynamic effects at the site of action. In a gas mixture at sea level, because atmospheric pressure is 101.3kPa, partial pressure (kPa) is often used interchangeably with fractional concentration (%). However, in solution, partial pressure cannot be equated to blood concentration because of wide variation in solubility. Gas solubility in blood is usually expressed as the blood–gas partition coefficient (BGPC), defined as the volume of gas dissolved in a unit volume of blood when at equilibrium with the gas alone. A more soluble drug (high BGPC) requires a greater number of molecules to be dissolved to exert a given partial pressure than a less-soluble one (low BGPC).

Exponential processes

Pharmacokinetic processes usually occur at a rate proportional to the concentration gradient at the time. As the process continues, the concentration gradient falls, thus progressively slowing the rate of change. This results in an exponential relationship between concentration and time and applies to most drug elimination and transfer between tissues.

Summary

Recommended drug doses are derived from average values in population studies and provide no certainty of response in a specific individual. Elimination half-life at steady state is of limited value in describing the recovery profile of a drug administered for a short period only. Context sensitive half-time provides more useful information under these circumstances. If a drug is given as a constant rate infusion, steady-state concentration will only be achieved after four to five half-lives. Partial pressure largely determines the behaviour of an inhaled drug. For maintenance of anaesthesia, a predictable steady state is easier to achieve with an inhalational agent than an intravenous one.

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There are two ways in which an exponential function can be described (Figure 2). If a specified time period is set, the decline is defined by the fraction by which the concentration has been reduced during this interval. This is the elimination rate constant (k), expressed as time^{-1} . Alternatively, a given fractional reduction in concentration is set, and the time taken to achieve this level is found. If a 50% reduction in concentration is used, the time taken is the half-life ($t_{1/2}$); this will be constant whatever starting drug concentration is used. Another time period that can be used to describe the curve is the time constant (τ). This is the point at which the elimination of drug would have been completed if the process had continued at its initial rate; it corresponds with a reduction in concentration to 37% of the original value.

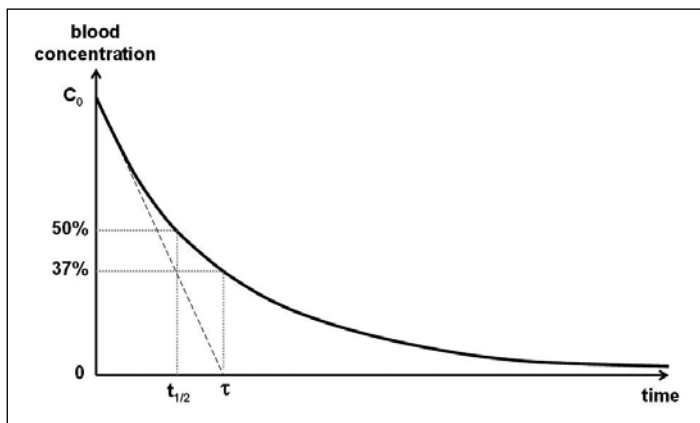


Figure 2. Exponential decline. C_0 initial concentration; $t_{1/2}$ half-life; τ time constant

Pharmacological compartments

Drugs are not distributed uniformly throughout the body. The speed with which a drug reaches a particular tissue is largely dependent on its local blood flow, and for analytical convenience, similar tissue types are often grouped together into various 'compartments' depending on their blood supply.

The capacity of each compartment to act as a reservoir for the drug is determined by a combination of its size and affinity for the drug. It is important to note that pharmacokinetic compartments are mathematical models and do not correspond to actual tissues; they are a concepts enabling the prediction of the pharmacokinetic behaviour of drugs. When performing mathematical modelling, it is likely that a lipid-soluble drug that is widely distributed is likely to have several compartments; a highly ionized drug that remains in the extracellular space is likely to be best described by assuming a one-compartment model. An example of a three-compartment model is shown in Figure 3; these correspond to vessel-rich, intermediate, and vessel-poor tissues, with a central compartment (blood), through which drugs must pass during uptake or elimination.

Because movement between compartments is dependent on the concentration difference between them, the process is exponential and the rate of transfer to the slower tissues decreases as they accumulate more drug.

Volume of distribution

When a drug has been fully distributed throughout the body and the system is at equilibrium, the volume within which

the drug is contained is called the volume of distribution at steady state (Vd_{ss}). It is a theoretical value expressed as the volume of blood which would be necessary to contain the entire drug present in the body, at the equilibrium concentration (units: l.kg^{-1}).

For a lipid-soluble drug (e.g. fentanyl) a litre of fat will hold many times more drug than a litre of blood, and thus its Vd_{ss} ($41.\text{kg}^{-1}$) will be much greater than the total body volume. In contrast, a highly ionized drug (e.g. glycopyrrolate) that does not readily cross lipid membranes has a Vd_{ss} of only 0.16l.kg^{-1} .

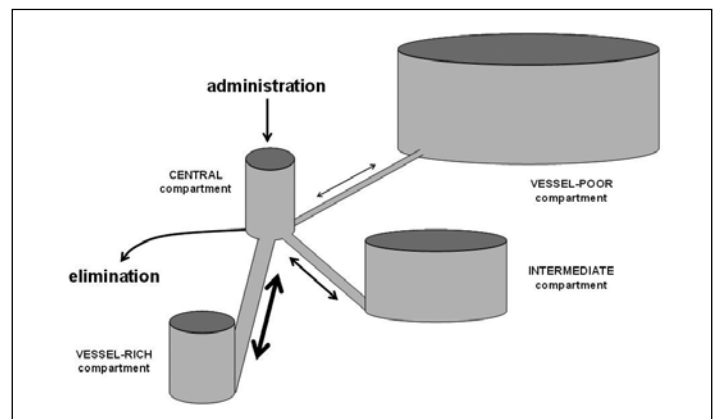


Figure 3. Illustration of a three-compartment model for a lipid-soluble drug. Pipe size represents blood flow and tank size the capacity as a drug reservoir

Clearance

Although a drug may be widely distributed throughout the body, it is usually removed only from the blood. Clearance (Cl) is a concept used to describe this, and it represents the volume of blood from which the drug is completely eliminated in unit time. For example, if the concentration in blood is reduced by 20% in an hour, the result is equivalent to removing the entire drug from 20% of the blood volume (1000ml), corresponding to a clearance of 1000ml.h^{-1} or 16.7ml.min^{-1} ; it is stated that clearance is also often adjusted for body weight.

A large elimination rate constant (k) produces a short elimination half-life ($t_{1/2}$); this will result from a high (Cl) or a small volume of distribution (Vd_{ss}).

PHARMACOKINETIC PATHWAY

In general, the passage of a drug through the body can be separated into three distinct phases: uptake, distribution, and elimination.

Uptake

Different routes of administration produce variability in the rate of drug uptake and amount of drug delivered effectively to the body. IV administration of a drug results in the entire dose entering the plasma immediately, although it must pass initially through the pulmonary circulation and some drugs (e.g. fentanyl) have significant take-up by the lungs.

Gastrointestinal (GI) administration requires the drug to cross the intestinal wall. The rate of absorption depends on surface area, pH, and, in some drugs, active systems. In general, unionized drugs (e.g. ethanol) are well absorbed throughout the intestine; absorption of

weak acids (e.g. aspirin) is facilitated by a low pH and weak bases (e.g. morphine) by a high pH. For drugs that remain completely ionized throughout the gut (e.g. glycopyrrolate), passive GI absorption is negligible.

Even after GI absorption, a drug may not reach the systemic circulation. Metabolism can occur in the gut mucosa (e.g. dopamine) or in the liver during its first pass via the portal vein (e.g. propranolol). This problem can be circumvented by administration at a site that avoids the portal circulation such as sublingual or, to some extent, rectal. The degree to which an administered drug reaches the systemic bloodstream is termed its bioavailability (Figure 4).

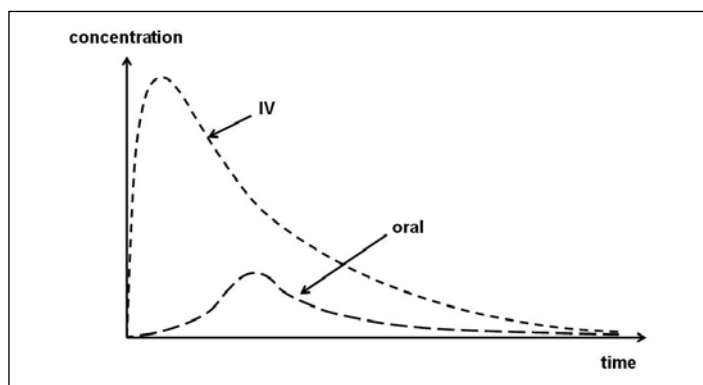


Figure 4. Oral bioavailability. Same dose administered IV and orally on separate occasions. Oral bioavailability = area under curve oral/area under curve IV

Uptake after intramuscular or subcutaneous administration is largely dependent on local blood flow rather than ionization or lipid solubility. The transdermal route can be used for highly lipid-soluble drugs (e.g. GTN, fentanyl), where slow absorption eventually produces sustained blood concentrations.

A fundamentally different pattern of uptake is seen for an inhaled drug in that it crosses the alveolar membrane into the blood along its partial pressure gradient. This produces an exponential wash-in, until at equilibrium (i.e. the partial pressure in blood equals that in the inspired and expired gas) no further net uptake occurs.

A clinical effect requires sufficient uptake to exert an adequate partial pressure in the body tissues; it is achieved most rapidly by a:

- high fractional concentration of inhaled drug
- high minute ventilation
- low BGPC.

The faster speed of onset produced by a low BGPC reflects the smaller number of molecules needed in solution to exert a partial pressure. A low cardiac output can also accelerate induction somewhat, with reduced perfusion to areas outside the vessel-rich group resulting in less drug needed to be taken up from the alveoli.

Alveolar partial pressure, measurable from end-tidal exhaled gas, closely reflects that of arterial blood and, in turn, that of the brain, enabling continuous monitoring of an indirect measure of drug delivery to the target site.

Distribution

After IV administration of a drug, the peak blood concentration is determined by the dose, the rate of administration, and the cardiac output. With a high cardiac output, the effective volume of blood in which the drug is initially diluted is larger, leading to a lower peak concentration. However, the high cardiac output transports the drug quickly to the vessel-rich tissues (including brain), and for highly lipid-soluble drugs, rapid equilibration occurs, leading to a fast onset of action. It is the high blood supply more than the lipid solubility that explains this.

Conversely, a low cardiac output leads to a higher initial peak concentration, because the drug is mixed with a smaller volume of blood during injection, though it will take longer to reach its target site. This explains why a smaller dose of induction agent is required in an elderly or shocked patient but may have a slower onset of action, while a young patient may require a much larger dose, yet will start to feel the effects more quickly.

Other tissues may also have a high affinity for the drug, but can only take up the drug slowly as they receive a lower proportion of the cardiac output. As they do so, however, the blood concentration decreases, soon falling below the brain concentration, whereupon the drug leaves the brain to be redistributed to other tissues. This redistribution is referred to as the α phase and explains the rapid termination of effect of lipid-soluble drugs such as propofol or thiopental following a bolus dose. As the less well-perfused tissues accumulate more drug, the concentration difference between compartments falls and the rate of redistribution slows in a declining exponential fashion. This also acts to slow down the redistribution if further drug is given, and subsequent doses should therefore be amended accordingly.

For inhalational agents, the pharmacokinetic model for distribution is similar; however, because the rate of administration is slower, the various compartments fill simultaneously, although at different rates depending on their blood supplies. Because there is never a rapid loading dose to any one compartment, redistribution between compartments is minimal. As administration continues, the vessel-poor and intermediate compartments become progressively saturated, delaying subsequent recovery, particularly for agents with a high lipid solubility.¹ Regardless of the period of administration, however, the partial pressure in any tissue will never exceed that administered.

Elimination

Although the initial effects of a drug may wear off because of redistribution, full recovery depends upon the removal of the drug from the body. Such elimination may result from excretion, metabolism, or a combination of both. Large molecular weight drugs are often excreted in the bile, but most drugs are renally excreted. In order for the kidneys to handle lipid-soluble drugs, they need to be metabolized into a polar, water-soluble form. Most of this metabolism occurs in the liver and can be divided into Phase 1 and Phase 2 reactions. Phase 1 reactions include oxidation, reduction, and hydrolysis; in Phase 2 reactions, the resulting metabolites are conjugated with sulphate, glucuronide, or other groups.

For most drugs, elimination occurs in an exponentially declining manner, the rate of elimination being proportional to the plasma

concentration, as the downstream end of the gradient remains at zero. This system (i.e. the amount of drug being removed is a constant fraction in unit time rather than a constant amount) is known as first-order kinetics.

For some drugs, elimination may depend on the action of an enzyme or transporters which can become saturated. Once the relevant blood concentration is reached, elimination becomes constant, limited to a maximum amount in unit time. This is referred to as zero-order kinetics and can result in dangerously high concentrations with continued, unmonitored drug administration. It may be encountered at high concentrations with aspirin, ethanol, phenytoin, or thiopental.

With inhalational agents (halothane excepted), minimal metabolism occurs and elimination is via the reverse process to uptake. Recovery is reliant on adequate ventilation, but its duration is usually more dependent on the extent of tissue saturation.

PRACTICAL APPLICATIONS

Establishing steady state

If a drug is given as a constant infusion, it will eventually reach a steady state (i.e. with the whole V_{dss} containing the drug at a stable concentration, and elimination occurring at the same rate as administration). It takes four to five elimination half-lives to achieve this.

The target concentration can be attained far more rapidly using an initial loading dose followed by further additional drug in a declining exponential fashion as redistribution to other tissues occurs. Computer-driven target-controlled infusion (TCI) systems deliver this pattern automatically,² adjusted for patient age, weight, and target concentration. Alternatively, this can be approximated closely using a stepped manual infusion scheme.³

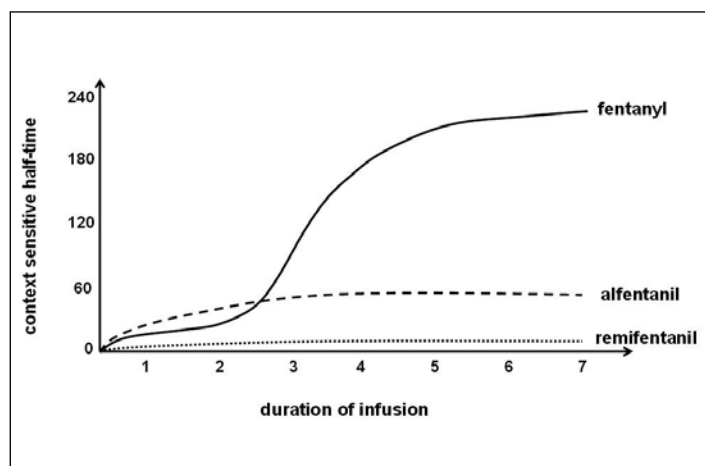


Figure 5. Context-sensitive half-times of fentanyl, alfentanil, and remifentanyl

Context-sensitive half-time

Elimination half-life relates to the decline in plasma drug concentration from steady state following distribution throughout the whole V_{dss} . It provides a useful guide to dosage intervals for longterm drug maintenance. However, in anaesthetic practice, few drugs are administered long enough to reach the steady state. The context-sensitive half-time (CST) then becomes a more useful descriptor,⁴ detailing the plasma half-life after an infusion of a specified duration (Figure 5).

For drugs such as fentanyl, in which redistribution is the main mechanism responsible for the decline in plasma concentration after a brief infusion or bolus, the CST will initially be short. As the duration of infusion continues, redistribution becomes progressively less important and the CST increases, until ultimately it equals the elimination half-life. For a drug with a small volume of distribution, such as remifentanyl, redistribution is very limited and the CST changes little even with prolonged infusion.

Predictability

Established pharmacokinetic and pharmacodynamic data are derived from averaged population studies. When based on these, even the most sophisticated dosage schemes for IV drugs will produce substantial variation in response between individuals, in both the blood/brain concentration (pharmacokinetics) and the subsequent effects (pharmacodynamics).⁵

In contrast, for inhalational anaesthetic agents, although pharmacodynamic variability will still occur, pharmacokinetic behaviour will be far more predictable, because of the physics of gas/vapour solution in a liquid. Indeed, at equilibrium the partial pressure of an inhalational agent in blood (and other tissues) will precisely equal that in the inhaled gas mixture. Furthermore, the end-tidal partial pressure of an inhalational agent can be measured in real-time, providing a value very close to that in arterial blood.

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Pharmacodynamics and Receptor Physiology

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INTRODUCTION

Pharmacodynamics describes the processes through which a drug brings about its effect in the body. To begin to comprehend this, we must start by breaking down the interaction to a molecular level and create models to further our understanding. The fundamental principle behind a drug's action is that to cause effect, it must interact with its target.

TARGETS

These are endogenous macromolecules which play some role in regulating the body's normal physiological processes. The word target is a generic term for the site where any individual drug creates its actions. They can be broadly classified into four types, depending on the function they normally serve:

1. **Receptors** e.g. adrenergic receptors targeted by adrenaline (epinephrine)
2. **Ion channels** e.g. voltage gated Na⁺ channels targeted by lidocaine
3. **Enzymes** e.g. Acetylcholinesterase targeted by neostigmine
4. **Carrier molecules** e.g. Noradrenaline (norepinephrine) uptake-1 targeted by tricyclic antidepressant drugs.

Confusion can arise at this point over the interchangeable use of the term '*receptor*'. The word receptor has been used as a general term for the molecular site of action of any drug (described here as a target) or more specifically as a cell membrane associated structure involved in the transduction of an endogenous signalling process (one particular target sub-type); the latter use is applied here. This account of pharmacodynamics will describe the general principles which apply to all drug-target interactions before moving on to the specific interactions a drug can have with a receptor.

DRUG-TARGET INTERACTION

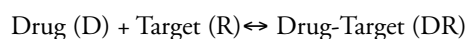
This implies a coming together of the drug with its target or more specifically a small part of the target. The drug's atomic configuration must allow it to bind with the target, analogous to a key (drug) fitting a lock (target). The need for this spatial symmetry explains

why individual isomers of the same drug can produce different effects – without the right shape the key will not fit the lock. The term binding represents the idea that the drug and target are now considered 'joined' and are no longer two separate entities. The exact nature of this adherence is not important other than its potential reversibility – the possibility they could exist separately again.

The binding process somehow induces a change in the behaviour of the target molecule, which brings about the drug's effects. In order to be clinically useful a drug needs to demonstrate specificity for the target it interacts with. It should be noted that drugs can bind to structures that are not in the four groups listed without producing clinical effects, and that there are drugs whose target has yet to be discovered. The majority of drugs can be assumed to work in this way although some produce their effects through physiochemical means alone.

DRUG-TARGET KINETICS

For reversible drug-target interactions a dynamic equilibrium exists:



This 'first principle' allows further manipulation to produce many mathematical formulae describing the concepts of pharmacodynamics.

The position of the equilibrium is described by K_D , the equilibrium constant (also referred to as the dissociation constant), which is the ratio of the dissociated forms to the associated form:

$$K_D = \frac{[D] \times [R]}{[DR]}$$

The affinity constant of a drug indicates how readily it will bind to its target and is the reciprocal of the equilibrium constant ($1/K_D$).

RECEPTORS

The human body has evolved multiple ways for communication within and between its own various

Summary

- Pharmacodynamics illustrates what a drug does to the body.
- Drugs act on 'targets' by binding.
- The equilibrium between bound and unbound targets (affinity) helps to determine a drug's effect.
- Receptors are a special type of target, involved in the body's normal signalling processes.
- Receptors can be activated, partially activated or inactivated when bound by a drug (efficacy).
- Plotting log drug dose against response produces curves which differ, depending on affinity, efficacy and the presence of other drugs.

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organ systems. Put very simply, signals are sent from one place and received in another which contributes to the maintenance of homeostasis, facilitating whatever change is necessary at that time.

Receptors are involved in the receiving and further processing (transduction) of these endogenous signals, and as such are one of the main targets for drugs, either by creating a signal which was not there naturally, through drug–receptor interaction, or acting as a blocker to the body’s own signals.

Generally they are proteins found in cell membranes that selectively interact via a specific binding site with a molecule from the extracellular environment (ligand). When these ligands occur naturally, binding to a specific receptor transmits the intended signal. One ligand may bind to multiple different receptor types bringing about contrasting effects at each.

There are four types of receptor, classified on their normal mode of action:

Ligand gated ion channels (Figure 1)

These receptors undergo a conformational change after the natural ligand binds to its recognition site on the extracellular portion of the receptor. This opens a pore in the cell membrane through which ions can travel. The exact nature of the ion depends on the receptor itself, the direction of travel being determined by the concentration gradient.

Nicotinic acetylcholine receptors found at the neuromuscular junction are an example. The binding of two acetylcholine molecules opens a non-selective cation channel which allows Na⁺ ions to flow in, down its large concentration gradient.

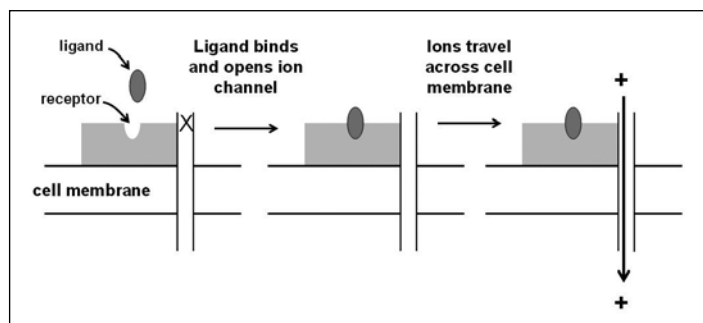


Figure 1. A ligand gated ion channel

G-protein coupled receptors (Figure 2)

These are receptors made of multiple associated sub-units which span the cell membrane. Again, activation begins with the attachment of a ligand to a specific extracellular binding site. This enables a change in the arrangement of the receptors constituent parts, which in turn, leads to an alteration in the activity of a specific intracellular enzyme (either adenylate cyclase or phospholipase C). The displacement of guanine diphosphate (GDP) by guanine triphosphate (GTP) from the receptor complex is integral to this process, hence the term ‘G-protein’. A change in enzyme activity will alter the concentration of the enzymes substrates, mediating the response to the initial signal. This is a much slower process which relies on 2nd messengers (the intracellular substances) to amplify the external signal, as part of a biological cascade.

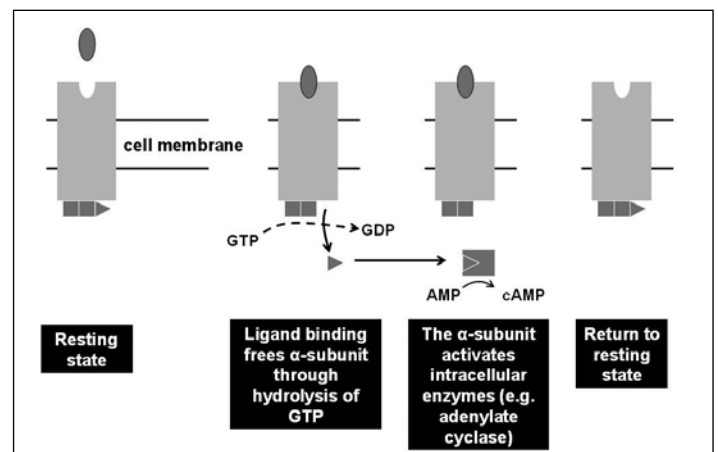


Figure 2. A G-protein coupled receptor

Tyrosine kinase receptors

These mediate the action of insulin and a variety of growth factors. Extracellular ligand binding activates intracellular tyrosine kinase, phosphorylating various target proteins.

Intracellular receptors

Lipid soluble ligands are able to cross the cell membrane and activate nuclear receptors which in turn alter DNA transcription. Steroid receptors are an example.

DRUG–RECEPTOR INTERACTIONS AND RESPONSE

The next section of this article describes examples to demonstrate the specifics of drug–receptor interactions.

In order to cause an effect, a drug’s first step is binding to its receptor and the second is inducing some form of change. The overall effect a drug can have will depend on the proportion of receptors available that are occupied (bound by) the drug; if all receptors are occupied, then that drug must be exerting its own maximum possible effect. The fraction of occupied receptors (f) can be described mathematically using the principles of drug–target kinetics, and dividing receptors to those occupied and those that are not:

$$\text{Total Receptors (Rt)} = \text{Free Receptors (R)} + \text{Drug-Receptor complexes (DR)}$$

This can be re-arranged to show that:

$$f = \frac{[D]}{K_D + [D]}$$

Figure 3 demonstrates this relationship graphically. As the drug concentration rises, the fraction of receptors occupied increases and approaches 1. This is an example of a rectangular hyperbola. Since response is directly proportional to the fractional occupancy, the y axis can be re-labelled as response, giving a dose-response curve. When half the receptors are occupied then the drug concentration is equal to the dissociation constant.

Another important concept is that of intrinsic activity, this describes the ability of the drug to produce a response from its receptor after it has bound. It is also known as efficacy and represents the magnitude of effect the drug can have, ranging from 0 (no effect) to 1 (maximal possible effect on that receptor). A drug which combines with its

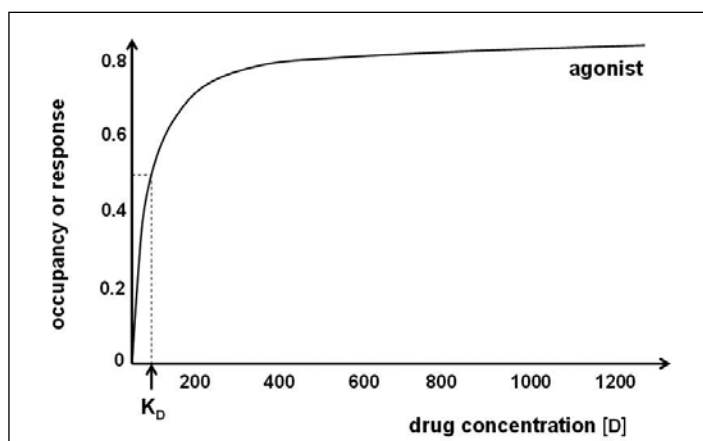


Figure 3. Dose response curve of an agonist at a receptor

receptor to give a maximal effect is an agonist - the 'key turns in the lock'. One which has no activity when bound but prevents the receptor being activated by other means is an antagonist - the 'key blocks the lock'. Any drug which produces a response, but less than the maximal response possible from that tissue is a partial agonist.

The response to a drug is therefore governed by the fraction of receptors occupied, combined with the drug's efficacy once bound.

Dose-response curves (Figure 4)

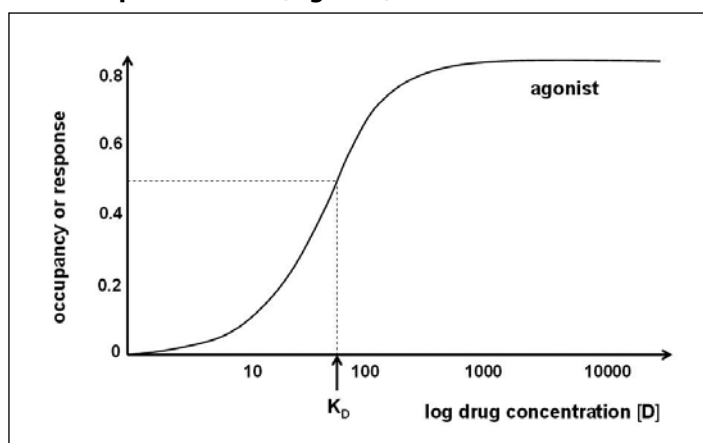


Figure 4. Log dose-response curve. Changing the x-axis to a log scale transforms the rectangular hyperbola of Figure 3 into a much more user friendly sigmoid shape, with an almost linear middle section

This curve can be used to demonstrate graphically all the various principles that underlie drug-receptor physiology - affinity, antagonism and partial agonism:

Affinity (Figure 5)

K_D , the dissociation constant, can be derived from the graph, as it equals the drug dose which gives 50% receptor occupancy. As some receptors bind more than one drug, differences in the affinity the drugs have for the receptor can be demonstrated. A drug with a lower affinity (but equal efficacy) has its log dose response curve shifted to the right. The two curves are parallel; for an equal amount of drug, a higher proportion of receptors are occupied by drug A than drug B, as A has a greater affinity. The same level of occupancy (and hence response) can be achieved with B, it just requires more drug to do so.

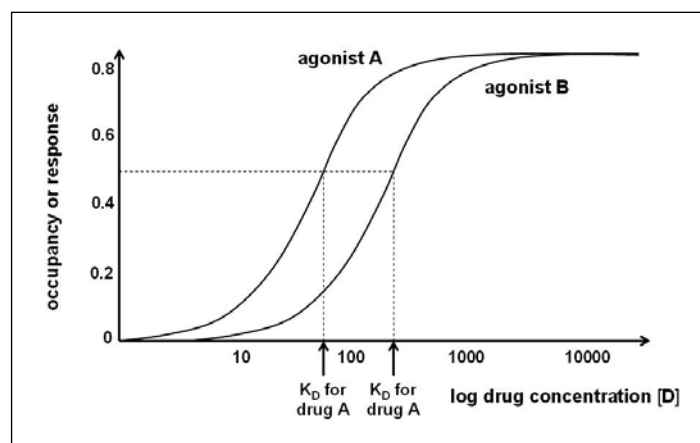


Figure 5. Log dose-response curve with varying affinity

Competitive antagonism

A similar situation can occur if there is competition for a receptor's binding site between agonist and antagonist drugs. In order to activate the receptor the agonist must bind as normal, but now it faces competition from the antagonist. The only effect the antagonist produces is to block the agonist, hence in the presence of an antagonist, more agonist must be added to illicit the same effect. Figure 6 shows that the conventional log-dose response curve for an agonist undergoes a parallel shift to the right when a fixed dose of competitive antagonist is added.

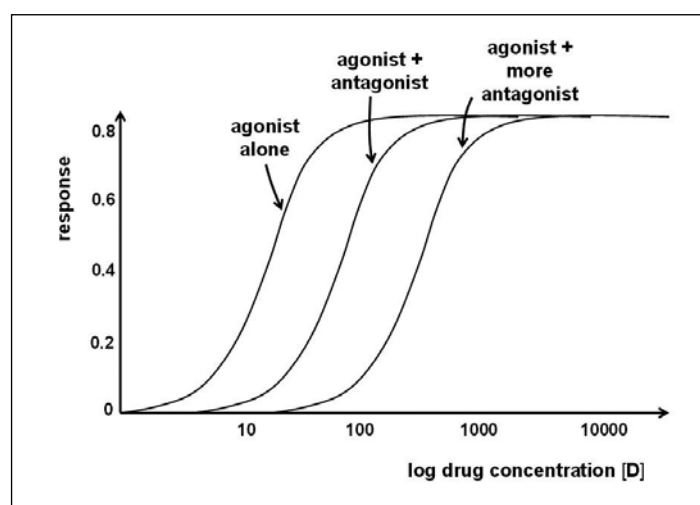


Figure 6. Log dose-response with competitive antagonism

Non-competitive antagonism

This occurs when an antagonist targets a different portion of the receptor to the agonist, and in doing so, somehow alters the receptors properties. The affinity the agonist has for its own binding site is the same but the effect the drug can have is now reduced. The agonist is not competing with the antagonist, so adding more agonist will never fully overcome its effect. Figure 7 shows that in the presence of a fixed dose of non-competitive antagonist the slope of the curve is flattened, but its position (K_D) remains the same.

Irreversible competitive antagonism

Up to now we have been talking about reversible drug-receptor

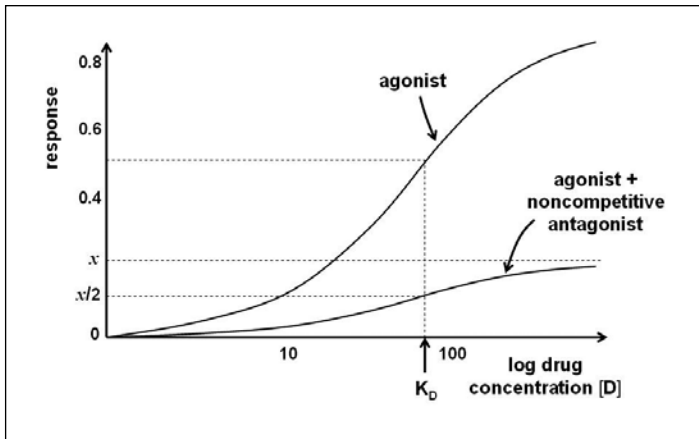


Figure 7. Log dose-response curve with non-competitive antagonism

interactions, but what happens when an antagonist binds a receptor and won't let go? This occurs if covalent bonds form, which are very strong and are not easily broken.

As the concentration of antagonist rises, more receptors become blocked irreversibly. This leaves fewer receptors for the agonist to work with, so its maximal effect is reduced permanently, as no amount of agonist can undo the antagonist-receptor bond. The affinity the agonist has for the remaining free receptors is unchanged. This is shown in Figure 8; there is a downward shift representing a reduced effect, but K_D remains the same.

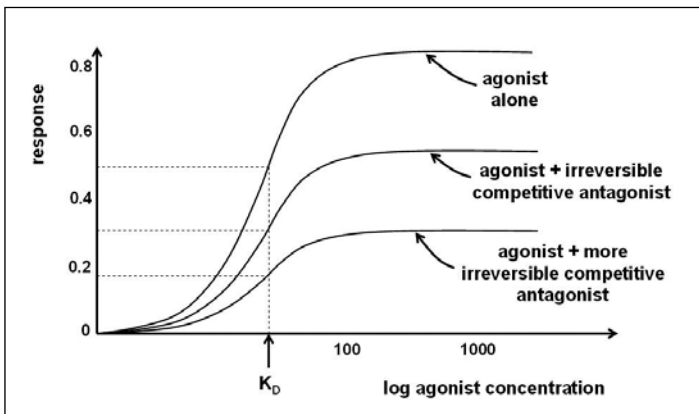


Figure 8. Log dose-response with irreversible competitive antagonism

Partial agonists

As previously defined, a partial agonist binds reversibly to a receptor eliciting an effect, but not the maximum possible effect. Different drugs can activate the same receptor but with varying efficacy. Figure 9 is a comparison of the log dose-response curves for an agonist and a partial agonist. The partial agonist can never generate a full response, so its final position will always be below that of the agonist. The two drugs could have the same affinity for their common receptor, but in general drugs that have a lower efficacy also have a lower affinity.

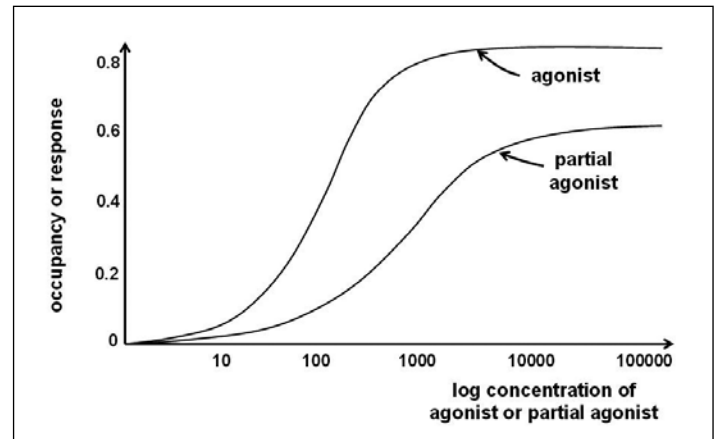


Figure 9. Log dose-response with partial agonist

When mixed together, a partial agonist and an agonist will compete for the same binding site, with the overall effect being dependant on which drug predominantly occupies the receptor. Figure 10 illustrates this situation by comparing the log dose-response curves for a partial agonist with four different (but constant) concentrations of agonist also present. As more partial agonist is added it occupies more of the receptors until the response seen is purely down to the partial agonist. If agonist activity was present to begin with, the response may be reduced by the addition of partial agonist as it competes with and replaces the agonist.

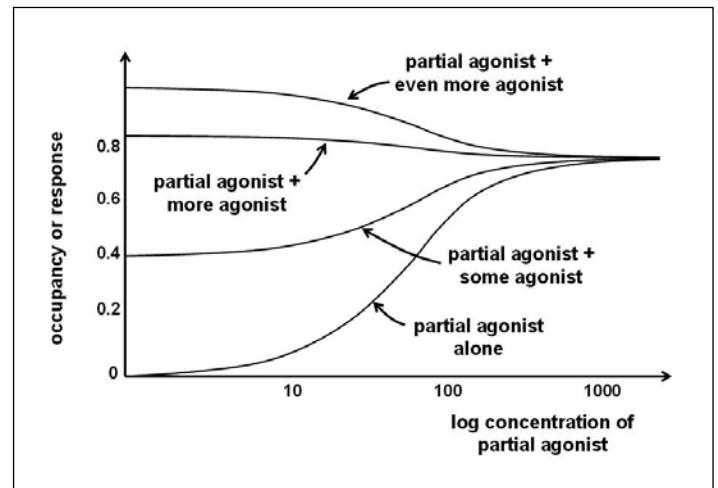


Figure 10. Log dose-response for partial agonist with agonist

SUMMARY

This classical theory provides a basis for understanding the relationship between binding and effect. There are many examples where this model does not fit and some of the ideas are not universally accepted. It is not the whole picture and should be seen as an introduction to the principles involved.

Originally published in *Anaesthesia Tutorial of the Week* (2007)

The Pharmacology of the Autonomic Nervous System

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Summary

A balance exists between sympathetic and parasympathetic outflow. Many common pathologies and surgical procedures can affect this balance, leading to disturbances in the function of organ systems. Drugs can contribute to autonomic disturbance, but drugs can also be used to redress the balance. Those acting on the ANS, tend to be agonists or antagonists at one or more of the various receptors, and this determines their clinical effects. Some have slightly different modes of action (such as the anticholinesterases or phosphodiesterase inhibitors) but still have marked effects on the ANS.

INTRODUCTION

In our article describing the anatomy and function of the autonomic nervous system (this edition, page 37), we saw that:

- The autonomic nervous system (ANS) reflexes are instrumental in the control of most of the body's organ systems.
- The afferent limb of these reflexes can be from the ANS or central nervous system (CNS). The efferent limb is mediated by the sympathetic (SNS) or parasympathetic (PNS) divisions, which are functionally and structurally distinct.
- The observed physiological effect will depend upon which neurotransmitter and types of receptors are involved.
- In the normal, resting situation equilibrium exists between sympathetic and parasympathetic activity. Drugs that stimulate or inhibit activity of either the parasympathetic or sympathetic division affect this balance.

TERMINOLOGY

Some common terminology is used to describe the action of drugs on the autonomic nervous system.

Sympathomimetics are drugs with similar actions to the postganglionic fibres of the SNS. They resemble epinephrine (adrenaline) in their actions and are also referred to as adrenergics or sympathetic agonists.

Sympatholytics are drugs that oppose the actions of the postganglionic fibres of the SNS. They are also referred to as antiadrenergics or sympathetic antagonists. Both groups are subdivided further depending on their actions on either alpha or beta- receptors.

Parasympathomimetics are agonists at postsynaptic muscarinic receptors. Their actions resemble acetylcholine and they are also referred to as cholinergics.

Parasympatholytics are drugs that oppose the actions of the PNS at the muscarinic receptors by blocking the actions of acetylcholine. They are also referred to as anticholinergics or vagolytics.

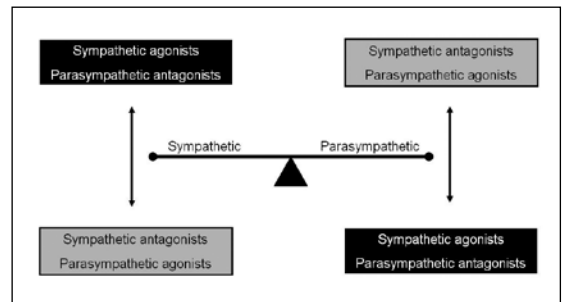


Figure 1. The effects of major drug groups on the 'autonomic equilibrium'

The autonomic effects of a drug may be the primary intended action – for example the sympathomimetic actions of dobutamine, or secondary effects – for example the parasympathomimetic action of repeated doses of succinylcholine.

In the remainder of this article, we will give an overview of the major groups of drugs that act on the autonomic nervous system and examine a few “special cases” - drugs that are commonly used in anaesthetic practice.

PHARMACOLOGY OF THE SYMPATHETIC NERVOUS SYSTEM

In our first article (this edition, page 37), we saw that most of the effects of the sympathetic nervous system are mediated by catecholamines (most commonly norepinephrine) acting at alpha or beta-adrenoreceptors. All adrenoreceptors are similar in structure and belong to the family of G-protein-coupled receptors.

α_1 -receptors activate phospholipase C and have their actions mainly by increasing release of intracellular calcium.

α_2 -receptors receptors inhibit adenylate cyclase, reducing cAMP formation.

β_1 and β_2 -receptors stimulate adenylate cyclase, increasing cAMP formation.

The main actions of these receptors are summarized in Table 1.

Drugs with agonist or antagonist effects at both types of adrenoreceptor are commonly encountered in anaesthetic practice, and the most important are discussed below.

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Table 1. Principal actions of sympathetic receptors

α_1-receptors	vasoconstriction, gut smooth muscle relaxation, salivary secretion, glycogenolysis in the liver, contraction of gut sphincters and uterus.
α_2-receptors	vasodilatation (central), vasoconstriction (peripheral), gut smooth muscle relaxation
β_1-receptors	positive inotropy and chronotropy
β_2-receptors	vasodilatation in muscle, gut and kidneys, bronchodilatation, pupillary dilatation, glycogenolysis

SYMPATHOMIMETICS

These drugs can be classified or grouped in a number of different ways, but perhaps the easiest is to classify them according to their actions on adrenoceptors. They either work by directly stimulating alpha and/or beta-receptors, or indirectly by stimulating the release of norepinephrine (noradrenaline) by acting presynaptically. A further class of drugs, the phosphodiesterase inhibitors, have a postsynaptic action.

α_1 -receptor agonists

Ephedrine

- An indirectly acting sympathomimetic, taken up into presynaptic nerve terminals displacing norepinephrine and resulting in alpha mediated vasoconstriction.
- Ephedrine also has a direct β -agonist effect increasing heart rate and cardiac output and blood pressure.
- These actions last for 10-15 minutes and repeated doses have a gradually decreasing effect (tachyphylaxis).
- Commonly used to treat the hypotension associated with subarachnoid (spinal) block.

Phenylephrine

- A directly acting α_1 -agonist causing vasoconstriction and increasing blood pressure, coronary and cerebral perfusion pressure.
- Heart rate usually slows due to reflex bradycardia. Cerebral and coronary blood flow are minimally affected.
- Used to treat hypotension associated with spinal and epidural anaesthesia and topically to provide vasoconstriction in the eye or nose before surgery.
- Large topical doses have been reported to cause significant CVS side effects including cardiac arrest.

Metaraminol

- Predominantly a direct α -agonist causing peripheral vasoconstriction. Also has indirect sympathomimetic actions caused by the release of norepinephrine and epinephrine.
- When used in the treatment of acute hypotension, a baroreceptor mediated bradycardia is frequently seen.

Amphetamine

- Causes CNS stimulation by releasing and blocking uptake of neurotransmitters. Also has peripheral indirect sympathomimetic activity causing acute rises in blood pressure.

- Currently, minimal therapeutic uses but derivatives of amphetamines are used as recreational drugs, for example ecstasy.

α_2 -receptor agonists

α_2 -receptors are found in the presynaptic membranes of adrenergic synapses and are widely distributed throughout the body including the CNS. They can be subdivided into three subtypes; α_{2A} (sedation, analgesia and sympatholysis), α_{2B} (vasoconstriction) and α_{2C} (CNS actions). Despite being agonists, their actions are generally more like sympatholytic drugs, but they are included here on the basis of their receptor activity.

Clonidine

- A potent α_2 -agonist acting on the receptors in the spinal cord. When given orally or IV results in dose dependent sedation, reduces the dose of induction drug needed, reduces the MAC of volatile anaesthetics and provides a degree of analgesia. It increases haemodynamic stability during surgery, at recovery from anaesthesia and may reduce cardiac morbidity in high-risk cases.
- It reduces shivering and oxygen consumption at recovery.
- When given epidurally, clonidine increases the quality and duration of block and provides a degree of postoperative analgesia. This practice has proved particularly popular in caudal epidurals in children. When used with local anaesthetics in spinals, it increases the duration and quality of block, but may increase the degree of hypotension. The need for a urinary catheter is reduced when compared to the use of intrathecal opioids.
- Clonidine has been used in critical care for sedation, analgesia for invasive procedures and to assist in reducing drug withdrawal symptoms after prolonged sedation.

Dexmedetomidine

- Has an even greater affinity for α_2 -receptors than clonidine. Many effects are similar to clonidine but there is less clinical experience.

β -receptor agonists

The main drugs in this group are the naturally occurring catecholamines, epinephrine and norepinephrine.

Epinephrine

- Predominantly β_1 and β_2 effects at low dose with increasing α effects at higher doses. Useful 'rescue inotrope' in resuscitation situations.

Norepinephrine

- α and β effects at very low dose, but α effects quickly predominate as dosage increases. Useful in vasodilatation (sepsis)

Dobutamine

- Potent β_1 -agonist. Some β_2 mediated vasodilatation is often seen, but occasionally matched by alpha mediated vasoconstriction. Useful in low cardiac output states.

Dopamine

- β_1 and dopamine-receptor agonism predominates at low dose. Increasing alpha effects seen as dose escalates.

Dopexamine

- Potent β_2 agonist with some dopamine receptor agonism. Positive inotropy and peripheral/splanchnic vasodilatation seen.

Isoprenaline

- The first synthetic β -receptor agonist for clinical use, stimulating both β_1 and β_2 receptors. Usually given as an infusion because of its short duration of action. Used mainly to treat bradyarrhythmias and as a bronchodilator. Now largely replaced as a bronchodilator by β_2 selective drugs because of the risk of cardiac arrhythmias.

Salbutamol

- Predominantly a β_2 -agonist used in the treatment of asthma, both intravenously and by inhalation. Also slows peristalsis and causes muscle tremor in large doses.

- Alternatives include terbutaline, and salmeterol and formoterol that are longer lasting.

Ritodrine

- β_2 -agonist used as a uterine relaxant (tocolytic) to prevent premature labour. Given IV initially followed by oral maintenance therapy. Salbutamol is also used for the same effect.

Phosphodiesterase Inhibitors

- Phosphodiesterase is the enzyme responsible for breakdown of the cAMP produced by β -receptor activation. Inhibition of phosphodiesterase leads to accumulation of cAMP, which acts to amplify a β -mediated sympathetic nervous system response. Various subtypes of phosphodiesterase are predominant in different cells and tissues and a number of different drugs exist which will predominantly inhibit the various subtypes. Whilst a full description is beyond the scope of this article, two of the most common drugs are mentioned below.

Theophylline/aminophylline

- Theophylline is a methylxanthine derivative, which is a non specific inhibitor of all the phosphodiesterase subtypes.
- Aminophylline is a mixture of theophylline and ethylenediamine, which improves solubility and hence allows intravenous administration.
- These drugs are predominantly used as bronchodilators, but other actions include weak positive inotropy, peripheral and coronary vasodilation, and a degree of CNS stimulation.

Table 2. Commonly used sympathomimetic drugs - routes of administration and doses

Drug	Route given	Dose given (average adult)	
		Bolus	Infusion
α-agonists			
Ephedrine	IV	3-6mg	0.5-5.0mg.min ⁻¹
	IM	10-20mg	
	Topically	0.5% solution	
Phenylephrine	IV	0.25-0.5mg	25-180mcg.min ⁻¹
	IM	2.0-5.0mg	
	Topically	0.25-1.0% (nasal)	
Metaraminol	IV	0.25-0.5mg	
	IM	2.0-5.0mg	
Methoxamine	IV	1.0-2.0mg	
	IM	5-10mg	
Clonidine	O	2-4mcg.kg ⁻¹	
	IV	1-4mcg.kg ⁻¹	
	Epidural	1-2mcg.kg ⁻¹	
	Intrathecal	1.0mcg.kg ⁻¹ (max)	
β-agonists			
Isoprenaline	IV	1-2mcg	2-4mcg.min ⁻¹
Salbutamol	IV	0.25mg	3-20mcg.min ⁻¹
	Inhaled (nebulised)	2.5-5.0mg	
Ritodrine	IV	10mg	50-350mcg.min ⁻¹
	IM	10mg	
	O		

- Theophyllines have a narrow therapeutic index, and dosage must be guided by monitoring of serum levels.

Enoximone

- A selective inhibitor of phosphodiesterase subtype III, enoximone is a potent inotrope, which also causes marked peripheral vasodilation.
- It is particularly effective in patients with a high background sympathetic tone, such as that seen in heart failure.
- Extensive first-pass metabolism means enoximone is only effective when given intravenously.

Other examples are amrinone and milrinone.

SYMPATHOLYTICS

These drugs block either α - or β -adrenergic receptors. It is also possible to have a sympatholytic action by blocking the sympathetic ganglia; only one drug is available to achieve this clinically (trimetaphan).

α -receptor antagonists (α -blockers)

Phenoxybenzamine

- A non-specific, irreversible α_1 - and α_2 -antagonist. The α_2 blockade leads to increased noradrenaline release and a beta receptor mediated compensatory tachycardia. Consequently non-specific alpha-blockers are often given concurrently with a beta adrenoceptor antagonist to block this effect (see below).
- Mainly used orally to induce hypotension, particularly in the management of pheochromocytoma.

Phentolamine

- Has similar CVS effects to phenoxybenzamine but the alpha blockade is shorter acting and reversible with alpha-agonists.

Prazosin and doxazosin

- Selective α_1 -antagonists which cause vasodilation and hypotension, but a lesser degree of compensatory tachycardia. Mainly used as adjuncts in the control of hypertension.

β -receptor antagonists (β -blockers)

Since they were first synthesized over 50 years ago, β -blockers have evolved into a large family of drugs. The drugs below are used to illustrate the key features of the differences between members of this family.

Propranolol

- Non-specific β_1 and β_2 -antagonist. Decreases heart rate, blood pressure and cardiac output.
- Increases airway resistance in patients with asthma and COPD and inhibits glucose metabolism, blocking sympathetic mediated 'warning signs' of hypoglycaemia in diabetics. May adversely affect lipid profile.
- Its main use now is in the control of thyrotoxicosis, treatment of essential tremor, migraine and control of the somatic manifestations of stress.

Atenolol, metoprolol

- Due to their predominance in blocking β_1 -receptors present in the myocardium they are often called 'cardioselective'. In reality, although cardioselective β -blockers have a predilection for β_1 receptors, at higher doses they become less specific, blocking both β_1 - and β_2 -receptors.
- β_1 -receptor blockade reduces heart rate, cardiac output, blood pressure and thus myocardial oxygen demand.
- In addition, a lusitropic action (an increase in diastolic time) increases coronary blood flow, useful in the treatment of hypertension and ischaemic heart disease.

Oxprenolol

- A relatively non-specific antagonist, blocking both β_1 - and β_2 -receptors but also with some partial β_2 -agonist action (intrinsic sympathomimetic activity). Thought to be therapeutically beneficial. Mainly used as an antihypertensive.

Esmolol

- A relatively specific β_1 -antagonist, esmolol is metabolised by red cell esterases and hence has a very short half-life. Its peak effects occur within 6-10 minutes of being given, but have almost completely disappeared by 20 minutes. It is only available for intravenous use.
- Useful for rapid control of hypertensive episodes such as those associated with tracheal intubation and for treatment of supraventricular tachycardias.

Sotalol

- A non-specific β -antagonist, which also has class III antiarrhythmic activity. Used for prophylaxis of paroxysmal supraventricular tachycardias and ventricular ectopics. May induce torsades des pointes in susceptible patients.

Labetalol

- A non-specific alpha and beta receptor antagonist. When given intravenously, the ratio of beta to alpha activity is approximately 7:1. Ideal for the control of acute hypertensive episodes, or for hypotensive anaesthesia.

Conflicting evidence has been published debating the proposed benefits of perioperative β -blockade in reducing the incidence of cardiac morbidity and mortality in high cardiac risk patients undergoing major surgery. Early enthusiasm for this has been dampened by recent evidence.¹

Ganglion blockers

This group of drugs acts by inhibiting the postsynaptic actions of acetylcholine at autonomic ganglia.

Trimetaphan

- The only drug in this group still in clinical use today. It causes profound peripheral vasodilatation and hypotension, reduces cardiac output and coronary and renal blood flow. It is very short acting and usually given by slow intravenous infusion to induce controlled hypotension.

- Causes a reflex tachycardia and tachyphylaxis is common. Not surprisingly, as a nicotinic antagonist it also causes some degree of non-depolarizing neuromuscular block.

PHARMACOLOGY OF THE PARASYMPATHETIC NERVOUS SYSTEM

Most of the effects of the parasympathetic nervous system are mediated through acetylcholine released from post-ganglionic nerve terminals and acting at muscarinic receptors. Muscarinic receptors are membrane-spanning protein structures which function as ion-channels. Several subtypes of muscarinic receptor have been identified, numbered M1-M5.

M1 receptors stimulate gastric acid secretion.

M2 receptors are thought to mediate the negative chronotropic effects of parasympathetic stimulation.

M3 receptors mediate lacrimal and salivary gland secretion, and may also be involved in gut smooth muscle contraction.

M4 and M5 subtypes are thought to be present mainly in the CNS, though M4 receptors may also mediate adrenaline secretion from the adrenal medulla.

Muscarinic receptors are the main target of drugs that act directly on the parasympathetic nervous system. In general though, both agonists and antagonists show little specificity for the different subtypes of muscarinic receptor.

PARASYMPATHOMIMETICS

Muscarinic receptor agonists

Direct acting muscarinic agonists are relatively infrequently used in clinical practice, but they are still used in a few specific cases.

Pilocarpine

- A semi-synthetic alkaloid and probably the most widely used

direct muscarinic agonist. Pilocarpine is mainly used topically in the treatment of glaucoma, but has been used systemically to treat xerostomia.

- Systemic effects include hypotension and bradycardia, bronchoconstriction, bronchorrhoea and sialorrhoea.

Acetyl-cholinesterase inhibitors

- As anaesthetists, we most commonly see parasympathomimetic actions of drugs following administration of the cholinesterase inhibitors during reversal of neuromuscular blockade. Hence it is appropriate to discuss this group of drugs (also known as anti cholinesterases) here. By non-specifically inhibiting the breakdown of acetylcholine in synapses, anti-cholinesterases will cause the desired improvement in neuromuscular transmission, but also widespread muscarinic receptor activation. This manifests itself as relative bradycardia, hypersalivation, increased gut smooth muscle activity and meiosis. These effects are usually counteracted by concurrent administration of a muscarinic antagonist, such as atropine or glycopyrrolate (see below).

Neostigmine

- The most commonly used anti-cholinesterase. Neostigmine is a carbamate ester, which reversibly inhibits acetyl cholinesterase by itself acting as a substrate. During this process, the acetyl cholinesterase molecule becomes carbamylated, and consequently inactive. Regeneration of the active enzyme occurs, but much slower than following hydrolysis of acetylcholine. It is available in a preparation combined with glycopyrrolate to minimise the muscarinic side effects.

Pyridostigmine

- Shares its mode of action with neostigmine. It has a slower onset of action, and a longer duration of action than neostigmine.
- It can be given orally, and is consequently useful in the treatment of myaesthesia gravis.

Table 3. Commonly used sympatholytic drugs - routes of administration and doses

		Dose given (average adult)	
Drug	Route given	Bolus	Infusion
α-antagonist			
Phenoxybenzamine	O IV	1-2mg.kg ⁻¹ daily	1mg.kg ⁻¹ (over 2hr)
Phentolamine	IV	1-5mg	
β-antagonist			
Propranolol	O IV	40-320mg.day ⁻¹ 1mg in 1min (max 5mg)	
Atenolol	O IV	25-100mg.day ⁻¹ 1mg.min ⁻¹ (max 10mg)	0.15mg.kg ⁻¹ over 20min
Esmolol		50mcg	50-200mcg.kg ⁻¹ .min ⁻¹
Labetalol		5-20mg (max 200mg)	2mg.min ⁻¹
Ganglion blocker			
Trimetaphan	IV	2-4mg.min ⁻¹	

Table 4. Commonly used parasympathomimetic drugs - routes of administration and doses

Drug	Route given	Dose given (average adult)	
		Bolus	Infusion
Muscarinic Agonists			
Pilocarpine	Topical (eye)	Titrated to effect	5mg 3 times per day
	Oral		N/A
Anti-Cholinesterases			
Neostigmine	IV	50-70mcg.kg ⁻¹	N/A
	Oral	15-30mg 4 times per day	
Pyridostigmine	Oral	0.3-1.2g in divided doses	N/A
Edrophonium	IV	2mg then 8mg (Tensilon test)	N/A
		500-700mcg.kg ⁻¹ (reversal)	

Edrophonium bromide

- Otherwise known as 'Tensilon' is most commonly used in the diagnosis of myasthenia gravis. It is a reversible competitive inhibitor of acetyl-cholinesterase, which prevents acetylcholine gaining access to the active site of the enzyme.
- The onset and duration of action of edrophonium are both significantly shorter than neostigmine (duration approximately 10 minutes).

PARASYMPATHOLYTICS**Muscarinic receptor antagonists**

- Muscarinic receptor antagonists are the drugs with a direct action on the parasympathetic nervous system, which are most frequently used in the anaesthetic setting. They are used both intra-operatively and as premedication, to treat symptomatic bradycardia and to reduce oropharyngeal and respiratory secretions.
- The most commonly used agents are atropine, glycopyrrolate and hyoscine. These are all competitive, reversible, non-specific antagonists, which produce dose dependant effects. At low dose, reduced salivation, sweating and bronchial secretion predominate. At higher doses, pupillary dilatation and tachycardia are seen. Still higher doses reduce gut motility, gastric secretion and bladder muscle function.

Atropine

- This naturally occurring tertiary amine is derived from the deadly nightshade plant (*Atropa belladonna*). It is lipid soluble and can therefore cross the blood brain barrier, causing central as well as peripheral effects. Peripheral effects tend to predominate and include tachycardia, bronchodilation and inhibition of sweating and salivation.
- Atropine is commonly used in an intravenous dose of 10-20mcg.kg⁻¹ to treat bradycardia during anaesthesia. A dose of 3mg will produce complete vagal blockade in an adult, but such a dose is generally restricted for use in resuscitation algorithms. Smaller doses are used as an anti-sialogogue.
- Atropine has been linked to post-operative confusion in the elderly, probably as a result of its central actions.

Hyoscine

- Is also a tertiary amine, and is particularly lipid soluble. Central effects thus tend to predominate – including drowsiness, amnesia and analgesia. It is also a powerful anti-sialogogue. These properties have seen hyoscine used frequently as premedication, but perhaps its most common use today is as an anti-emetic.
- It is particularly common in many proprietary travel sickness remedies.

Table 5. Commonly used parasympatholytic drugs - routes of administration and doses

	Route given	Dose given (average adult)	
		Bolus	Infusion
Atropine	IM/IV Oral	0.015-0.02mg.kg ⁻¹ 3mg for total vagal blockade 0.2-0.6mg	
Glycopyrrolate	IM/IV	0.2-0.4mg	
Hyoscine	SC/IM Oral Transdermal	0.2-0.6mg (pre-med) 0.3mg 6hrly (nausea) Releases 1mg.72hr ⁻¹ patch	SC 0.6-2.4mg per 24hrs to reduce secretions in palliative care setting
Ipratropium	Aerosol Nebulised	20-80mcg 6hrly 100-500mcg 6hrly	

Glycopyrrolate

- A synthetic quaternary amine. Glycopyrrolate is strongly ionised and therefore unable to cross the blood-brain barrier. Consequently it has no central effects, and is thus an alternative to atropine in the elderly patient.
- It is a more potent anti-sialogogue than atropine, but has slightly weaker cardiac effects. This makes it an ideal agent to be used in conjunction with the anti-cholinesterases, when salivation can be controlled without precipitating potentially harmful tachycardia.

Ipratropium

- Synthetic derivative of atropine, administered by nebulisation, or metered dose aerosol inhaler in the treatment of asthma.

- Competitive inhibition at muscarinic receptors on bronchial smooth muscle cells reduces bronchospasm, and there may also be a secondary effect reducing mast cell degranulation (which is muscarinic receptor mediated).
- Some systemic absorption may lead to mild tachycardia and increased cardiac output.

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Originally published in *Anaesthesia Tutorial of the Week* (2007)

Intravenous Drugs used for the Induction of Anaesthesia

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Summary

The agents available for induction of anaesthesia are described, with discussion of the advantages and disadvantages of each. Personal preference and familiarity of the practitioner largely determines the choice of agent, but it is important to maintain a broad knowledge of all available agents, for situations when the choice must be tailored to individual patient's requirements.

INTRODUCTION

These are drugs that, when given intravenously in an appropriate dose, cause a rapid loss of consciousness. This is often described as occurring within 'one arm-brain circulation time' that is simply the time taken for the drug to travel from the site of injection (usually the arm) to the brain, where they have their effect. They are used:

- To induce anaesthesia prior to other drugs being given to maintain anaesthesia
- As the sole drug for short procedures
- To maintain anaesthesia for longer procedures by intravenous infusion
- To provide sedation.

The commonest drugs currently in use can be classified according to their chemical structure and include:

- Barbiturates
- Phenols
- Imidazoles
- Phencyclidines
- Benzodiazepines

The most commonly used examples of each class will be discussed below.

FROM INDUCTION TO WAKE UP: WHAT HAPPENS TO A BOLUS OF IV INDUCTION DRUG?

On entering the blood stream, a percentage of the drug binds to the plasma proteins, with the rest remaining unbound or 'free'. The degree of protein binding will depend upon the physical characteristics of the drug in question – such as lipid solubility and degree of ionization. The drug is carried in the venous blood to the right side of the heart, through the pulmonary circulation, and via the left side of the heart into the systemic circulation.

The majority of the cardiac output (70%) passes to the brain, liver and kidney (often referred to as 'vessel rich organs'); thus a high proportion of the initial bolus is delivered to the cerebral circulation. The drug then passes along a concentration gradient from the blood into the brain. The rate of this transfer is dependent

on a number of factors:

- arterial concentration of the unbound free drug
- lipid solubility of the drug
- degree of ionization.

Unbound, lipid soluble, unionized molecules cross the blood brain barrier the quickest. Once the drug has penetrated the CNS tissue, it exerts its effects. Like most anaesthetic drugs, the exact mode of action of the intravenous drugs is unknown. It is thought that each drug acts at a specific receptor – GABA_A, NMDA and acetylcholine receptors have all been studied as potential sites of action.

Following the initial flooding of the CNS and other vessel rich tissues with non-ionized molecules, the drug starts to diffuse into other tissues that do not have such a rich blood supply. This secondary tissue uptake, predominantly by skeletal muscle, causes the plasma concentration to fall, allowing drug to diffuse out of the CNS down the resulting reverse concentration gradient. It is this initial redistribution of drug into other tissues that leads to the rapid wake up seen after a single dose of an induction drug. Metabolism and plasma clearance have a much less important role following a single bolus, but are more important following infusions and repeat doses of a drug.

Figure 1 demonstrates that fat, with its poor blood supply (vessel poor tissues), makes little contribution to the early redistribution of free drug following a bolus. However, following repeat doses or infusions, equilibration with adipose tissue forms a drug reservoir, often leading to a delayed wake up.

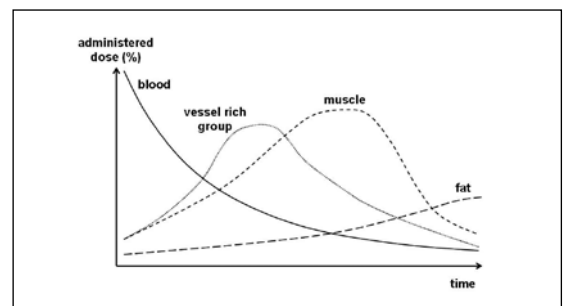


Figure 1. Graph of drug distribution in various tissues against time after an intravenous dose of thiopentone

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HOW IS THIS DIFFERENT IN STATES OF REDUCED CARDIAC OUTPUT?

In circumstances when cardiac output is reduced, for example after major blood loss, the body compensates by diverting an increased proportion of the cardiac output to the cerebral circulation. This preservation of cerebral blood flow in these situations is paramount. Thus a greater proportion of any given drug will enter the cerebral circulation. As a result, the dose of induction drug must always be reduced. Furthermore, as global cardiac output is reduced, the time taken for an induction drug to reach the brain and exert its effect is prolonged. The slow titration of a reduced dose of drug is the key to a safe induction in these patients.

THE PROPERTIES OF AN IDEAL IV INDUCTION DRUG

A number of properties, both physical and pharmacological (pharmacokinetic and pharmacodynamic) will be beneficial when designing an ideal intravenous anaesthetic drug. We will now look at these properties, and then see how our commonly used drugs compare.

Physical properties

- Water soluble & stable in solution
- Stable on exposure to light
- Long shelf life
- No pain on intravenous injection
- Painful when injected into an artery
- Non-irritant when injected subcutaneously
- Low incidence of thrombophlebitis
- Cheap.

Pharmacokinetic properties

- Rapid onset in one arm-brain circulation time
- Rapid redistribution to vessel rich tissue
- Rapid clearance and metabolism
- No active metabolites.

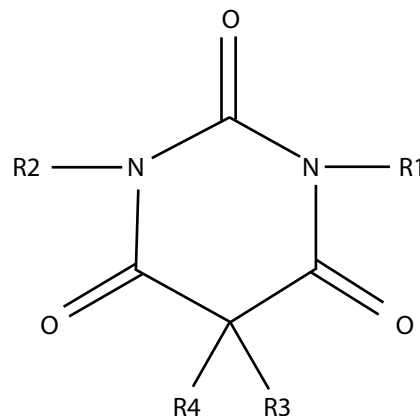
Pharmacodynamic properties

- High therapeutic ratio (ratio of toxic dose : minimally effective dose)
- Minimal cardiovascular and respiratory effects
- No histamine release/hypersensitivity reactions
- No emetic effects
- No involuntary movements
- No emergence nightmares
- No hang over effect
- No adrenocortical suppression
- Safe to use in porphyria.

PROPERTIES OF SPECIFIC IV INDUCTION DRUGS

The ampoule sizes, contents and concentrations reflect that commonly available within Europe. It is important to check what is available locally.

Sodium thiopental (thiopentone)



Thiopental (also referred to as thiopentone and Pentothal) is a barbiturate, supplied as a hygroscopic (attracts moisture from the atmosphere) pale yellow powder. Ampoules commonly contain 500mg of sodium thiopental with 6% sodium carbonate in an inert atmosphere of nitrogen. Reconstituted with 20ml of water this yields a 2.5% solution (25mg.ml⁻¹) with a pH of 10.8. The alkaline solution is bacteriostatic and safe to keep for 48 hours. The molecular structure of thiopental is based upon the barbiturate ring – as shown above. A sulphur atom at the carbon R2 position confers the short duration of action.

A dose of 4-5mg.kg⁻¹ of thiopentone produces a smooth onset of hypnosis with good definitive endpoints within 30 seconds of intravenous injection. Recovery after a single dose is rapid due to redistribution and there is a low incidence of restlessness and nausea and vomiting.

Thiopentone is 65-85% protein bound in plasma. Metabolism is slow and occurs in the liver. Excretion of metabolites occurs mainly in the urine. Following repeated doses or infusions of thiopental, metabolism follows zero order kinetics; this means that a constant amount of drug is being eliminated per unit time, irrespective of the plasma concentration. Some drugs are metabolized by first order kinetics; a constant fraction of drug is eliminated per unit time, i.e. dependant on plasma concentration. Zero order kinetics occur when the metabolic pathways become saturated leading to an accumulation of the active drug and delayed recovery.

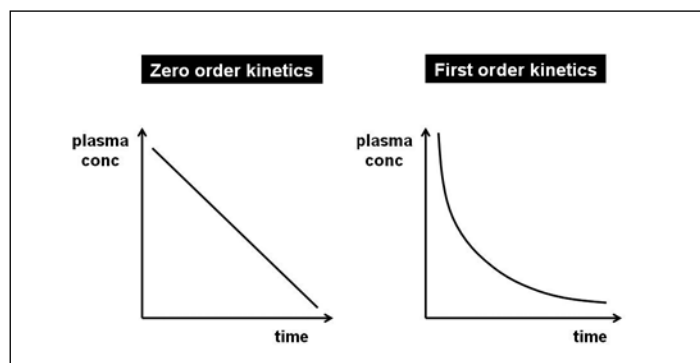


Figure 2. Graphs to show the characteristics of zero and first order kinetics

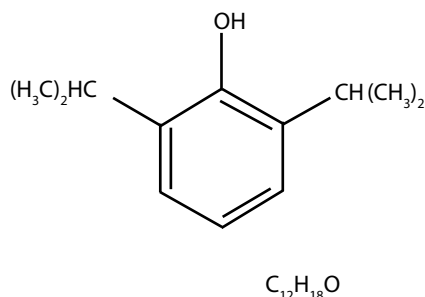
Thiopentone directly depresses the contractile force of the heart, reducing cardiac output and blood pressure. There may be a compensatory increase heart rate. It also decreases venous tone, causing pooling of blood in the peripheral veins; increasing the degree of hypotension, particularly in patients who are hypovolaemic (e.g. following haemorrhage).

Respiratory depression is common and a period of apnoea is usually seen following a bolus dose. Airway reflexes are well preserved in comparison with propofol which makes thiopentone unsuitable for use when inserting a laryngeal mask airway (LMA) which may cause coughing and laryngospasm. Histamine release can occur which may precipitate bronchospasm.

Thiopentone reduces cerebral blood flow, cerebral metabolic rate and oxygen demand. It has potent anticonvulsant properties. Following traumatic brain injury, an infusion of thiopentone to produce a "barbiturate coma" lowers intracranial pressure and may improve neurological outcome. This is however associated with significant accumulation, causing a prolonged effect with the potential for multiple complications.

The porphyrias are a group of disease characterised by overproduction and excretion of porphyrins (intermediate compounds produced during haemoprotein synthesis). Acute attacks may be precipitated by drugs, stress, infection, alcohol, pregnancy and starvation. Thiopentone may precipitate porphyria due to hepatic enzyme induction in susceptible patients, and hence it should be avoided.

Propofol (2,6 di-isopropylphenol)



Propofol is usually presented as a 1 or 2% aqueous emulsion (tiny fat droplets in suspension, hence the white colour) containing soya oil, egg phosphatide and glycerol. It is isotonic to plasma and has a pH of 7.0 - 8.5. It can cause pain on injection into small veins.

It is a short-acting general anaesthetic drug, with an onset of action of approximately 30 seconds. Recovery from anaesthesia is usually rapid. A smooth induction of anaesthesia usually follows a dose of 2-2.5mg.kg⁻¹. Propofol should be titrated against the response of the patient until the clinical signs show the onset of anaesthesia. The best endpoint is loss of verbal contact with the patient.

Following an IV bolus, there is rapid equilibration between the plasma and the highly perfused tissue of the brain as described earlier. Plasma levels decline rapidly as a result of redistribution, followed by a more prolonged period of hepatic metabolism and renal clearance. The initial redistribution half-life is between 2 and 4 minutes. Moderate hepatic or renal impairment does not alter the pharmacokinetics of propofol.

Propofol causes the most marked fall in blood pressure of all the induction drugs. This is mainly due to systemic vasodilatation. There may be an accompanying slight increase in heart rate. The fall in blood pressure is dose dependent and is most marked in the elderly and in shocked patients. This can be minimized by slow injection – avoiding inadvertent overdose.

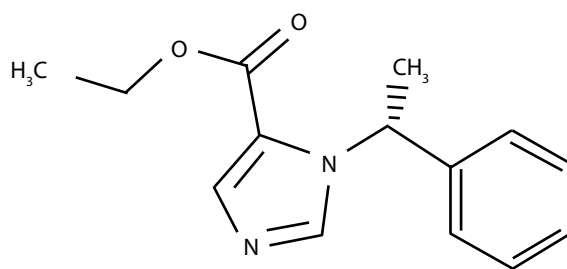
With the exception of ketamine, all induction drugs act on the respiratory centre to cause respiratory depression. This effect is the most profound with propofol and a period of apnoea is usually seen. Propofol also markedly reduces airway and pharyngeal reflexes, making it the ideal drug to use with the laryngeal mask.

Although propofol has been associated with epileptiform movements during induction and recovery, these movements must not be confused with true seizure activity. In practice, propofol is an anticonvulsant in normal doses. It has also been shown to reduce cerebral blood flow, metabolic rate and intra-cranial pressure.

An infusion of propofol is used commonly to provide sedation for adult patients undergoing minor procedures and on the intensive care unit. It is also the most commonly used drug to provide total intravenous anaesthesia, TIVA. A number of infusion regimes are widely used, but detailed discussion is beyond the scope of this tutorial. Propofol infusion is contraindicated for sedation in children due to concerns regarding its safety. A 'propofol infusion syndrome' has been described; effected children developing metabolic acidosis, lipidaemia, cardiac arrhythmias and an increased mortality.

Experience suggests propofol is safe to use in patients susceptible to porphyria.

Etomidate



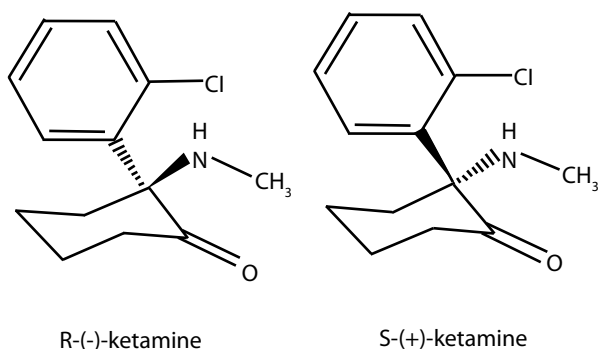
Etomidate is an imidazole ester. It is usually presented as a lipid emulsion or as a clear solution containing propylene glycol at a concentration of 2mg.ml⁻¹. Pain on injection is common and thrombophlebitis is a well-recognised complication in the postoperative period. The standard induction dose is 0.3mg.kg⁻¹, and recovery is rapid due to redistribution to muscle and fat. Induction of anaesthesia can be accompanied by involuntary movements which may be mistaken for generalized seizure activity. Recovery is frequently unpleasant and accompanied by nausea and vomiting.

It is rapidly metabolized by hepatic and plasma esterases to yield inactive metabolites. Excretion is predominantly urinary and the elimination half life varies from 1 – 5 hours. Etomidate causes the least cardiovascular depression of the IV anaesthetic drugs, with only a small reduction in the cardiac output and blood pressure.

In the past, etomidate was widely used to induce anaesthesia in the shocked, elderly or cardiovascularly compromised patient. However, more recently it has become less popular (see below). Etomidate causes transient apnoea, though less so than other drugs, and can cause cough or hiccups. Thus like thiopental, it is not ideally suited to use with the LMA. Post operative nausea and vomiting is common after etomidate administration.

Etomidate inhibits 11- β -hydroxylase, an enzyme important in adrenal steroid production. A single induction dose blocks the normal stress-induced increase in adrenal cortisol production for 4-8 hours, and up to 24 hours in elderly and debilitated patients. Continuous infusion of etomidate for sedation in critically ill patients has been shown to increase mortality. Although no increase in mortality has been identified following a single dose during induction of anaesthesia, the use of etomidate has declined in recent years due to a perceived potential morbidity.

Ketamine



Ketamine is a derivative of phencyclidine, a dissociative drug formerly used as an anaesthetic agent, which exhibited hallucinogenic and neurotoxic effects. A dissociative drug is one which reduces signals to the conscious mind from other parts of the brain, typically the senses. Ketamine can take the form of two stereo-isomers, R- and S-ketamine, as shown above. Stereoisomers are molecules in which the same atoms are bonded together in the same order, but they show a different 3D arrangement in space making them non-superimposable (they are often referred to as 'mirror images' of each other). It is usually presented as a racemic mixture of the 2 stereoisomers, but S-ketamine has recently become available due to its more desirable pharmacological properties.

The R- and S-ketamine isomers exhibit pharmacological and clinical differences. S-ketamine is three times as potent as R-ketamine and the recovery time and psychomimetic sequelae are reduced. This may however be a consequence of the reduced dose requirement required with the more potent S-ketamine.

Ketamine is prepared in a slightly acidic solution (pH 3.5–5.5) containing 10, 50 or 100mg.ml⁻¹. Standard ampoules also contain a preservative which prevents intrathecal or epidural use. It is also available as a powder for reconstitution.

Ketamine has hypnotic, analgesic and local anaesthetic properties. Its effects are mediated primarily by noncompetitive antagonism at the N-methyl-D-aspartate (NMDA) receptor in the brain and spinal cord.

Other mechanisms of action of ketamine may include an interaction with opioid receptors; however naloxone does not antagonize the analgesic effects of ketamine in humans.

Ketamine produces so-called 'dissociative' anaesthesia. This unique clinical state is typified by catalepsy in which the eyes may remain open with a slow nystagmic gaze and the corneal and light reflexes remain intact. Varying degrees of hypertonus and occasional purposeful movements unrelated to painful stimuli can be seen, even during adequate surgical anaesthesia.

Psychic sensations including alterations in mood state, floating sensations, vivid dreams and hallucinations are common during emergence from ketamine anaesthesia. These usually disappear on full waking. Benzodiazepine premedication reduces this emergence delirium.

Ketamine is unique amongst induction drugs in that it can be administered IV, IM, orally, nasally, rectally, and the preservative-free solution epidurally. The dose depends on the route of administration and the desired therapeutic effect. For induction of anaesthesia a dose of 0.5–1.5mg.kg⁻¹ can be given IV, or 4–10mg.kg⁻¹ IM. The onset of action is slower than other induction drugs (unconsciousness in 1-2min for IV use), and the end point may be difficult to judge with patients staring into the distance for a short period of time. The duration of action of a single dose is approximately 5-10 minutes.

Ketamine is metabolised in the liver, and conjugated metabolites are excreted in the urine. The elimination half life is 2.5 hours. Ketamine has a unique combination of cardiovascular effects. Its administration, unlike other induction drugs, is usually associated with tachycardia, increased blood pressure, and increased cardiac output. This makes ketamine useful in the shocked, unwell patient. Ketamine has a minimal effect on central respiratory drive, although a transient decrease in ventilation can occur after bolus administration. This, coupled with the fact that the protective airway reflexes remain relatively preserved, makes ketamine the ideal anaesthetic drug to be used in the prehospital environment. It does however increase salivation which can lead to upper airway obstruction. Salivation can be reduced by premedication with antimuscarinic drug such as glycopyrrolate. Ketamine is a bronchial smooth muscle relaxant, and therefore has a special role in the management of severe asthma.

In the past, ketamine was thought to increase cerebral blood flow and intracranial pressure, thereby limiting its use in patients with a head injury. However, providing hypoventilation and hypercapnia are avoided, this does not occur and there is some evidence that ketamine may have some cerebral protective effects via its action on NMDA receptors. Ketamine is thought to be safe to use in porphyria.

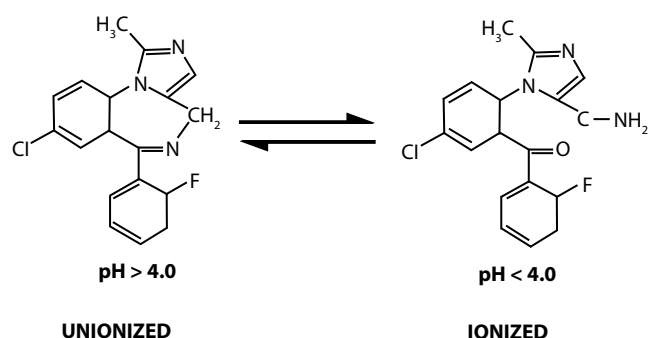
BENZODIAZEPINES

Although not strictly intravenous induction drugs, the pharmacokinetics of midazolam allow it to be used to induce anaesthesia. Diazepam is far more widely available than midazolam in poorly resourced settings and, even though its pharmacological properties are less suitable, it is commonly used to induce (or 'co-induce') anaesthesia.

Midazolam

Midazolam is a water soluble benzodiazepine. It comes as a clear

solution, usually at a concentration of 2mg.ml⁻¹. Midazolam exhibits a form of isomerism known as tautomerism. In the ampoule, as an acidic solution, the molecule exists in an ionized form. At physiological pH the molecule changes to become a highly lipid soluble unionized ring, accounting for its rapid onset of action. It does not cause pain on injection.



Like other benzodiazepines, midazolam acts at specific receptors closely allied to the GABA_A receptor. Activation of the benzodiazepine receptor increases chloride influx to neuronal cells via the GABA_A receptor, causing neuronal hyperpolarisation and the clinical effects seen.

Midazolam is usually used for sedation at a dose range of 0.05-0.1mg.kg⁻¹ (IV). Its advantage in this setting is its short duration of action and amnesic properties. In children it is useful as premedication - 30 minutes preoperatively at an oral dose of 0.5mg.kg⁻¹. It can be used as a sole IV induction drug, at a dose of 0.3mg.kg⁻¹, but its duration of onset is slow, limiting its use. Its duration of action is around 30 minutes which is longer than that of the other induction drugs. It undergoes hepatic metabolism and renal elimination. In the elderly, the lower hepatic blood flow and metabolic activity result in a significantly prolonged half life.

Midazolam has mild cardiovascular and respiratory depressant effects, so monitoring is important during sedation. When used as a sole induction drug, midazolam causes apnoea in up to 70% of patients. The effects of midazolam can be reversed with flumazenil, a competitive benzodiazepine antagonist. This should be given by intravenous injection in 100mcg increments and should act within 2 minutes. Flumazenil must be used cautiously, as it can cause agitation and seizures.

Diazepam

Diazepam is exclusively lipid soluble, due to its carbon-containing ring structure. This property makes it rapidly absorbed by the oral route but also means that it must be formulated as a lipid emulsion (diazemuls) for intravenous use. It is not an ideal agent for induction of anaesthesia but is included here because it is used for induction of anaesthesia in theatre and the critically ill in resource-poor settings, where more suitable agents may not reliably be available. In these settings diazepam is more widely used as an agent for procedural sedation and for sedation of the critically ill.

Diazepam has a long half-life and the wake-up time after single doses can be prolonged. When used as an infusion or six-hourly intramuscular doses for sedation in the Intensive Care Unit, accumulation means that the time for clearance of the drug may be several days. In addition, diazepam is metabolised in the liver to oxazepam and temazepam, which are also active 1,4-benzodiazepines. The long interval between doses has advantages where infusion devices are not available, particularly where staffing levels are stretched.

Diazepam also has a role in seizure control and in the management of alcohol withdrawal. The dose in children is 0.2-0.3mg.kg⁻¹ when administered intravenously and 0.5 mg.kg⁻¹ PR.

Diazepam causes cardiorespiratory compromise, particularly when co-administered with opioids. Diazemuls is less irritant to veins than the other lipid formulations.

CONCLUSION

The range of agents available for induction of anaesthesia has been described. The choice of agent is determined by the preference and familiarity of the anaesthetist, taking into account the suitability of each individual patient, requiring a particular procedure, by a particular surgeon. Choice of agent is also influenced by the availability of each agent in resource-poor settings.

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Pharmacology of Inhalational Anaesthetics

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Summary

Inhalational anaesthetics produce loss of consciousness, but may have other effects including analgesia (nitrous oxide) or muscle relaxation (isoflurane). They are presented as liquefied gases under pressure or as volatile liquids.

MODE OF ACTION

The molecular basis of inhalational anaesthesia is not fully understood. Historically, the first observation that had a significant impact was the Meyer-Overton hypothesis which demonstrated that the potency (expressed as minimum alveolar concentration, MAC - see below) of an anaesthetic agent increased in direct proportion to its oil:gas partition coefficient (see Figure 1). This led to the interpretation that the site of action of general anaesthetics was the lipid bilayer of nerve membranes and that when a sufficient amount of drug was dissolved in this layer, then anaesthesia occurred. There were several theories as to the molecular mechanism, but each with its own limitations.

More recent research suggests that inhalational agents may act on specific membrane proteins and alter ion flux or receptor function. This is supported by the fact that anaesthetic enantiomers (optical isomers) usually display different anaesthetic potencies in animals. The prime candidates for protein targets are:

GABA_A receptors - potentiation of GABA at this receptor occurs with halothane, isoflurane and sevoflurane.

Glycine receptors - these are often at the same CNS sites as the GABA_A receptors and are of particular

importance in lower brain centres and the spinal cord. Potentiation of glycine receptors is seen at low concentrations for all the volatile agents.

Two-pore-domain potassium channels - these have subunits that are activated by volatile and gaseous anaesthetics and may modulate membrane excitability and have a complex distribution within the CNS. Other possible targets may include NMDA receptors, HCN channels and some subtypes of the sodium channel.

POTENCY

The potency of an inhalational anaesthetic agent can be measured by its MAC. This is defined as the minimum alveolar concentration at steady-state that prevents reaction to a standard surgical stimulus (skin incision) in 50% of subjects at 1 atmosphere. MAC is affected by a wide range of physiological and pharmacological factors (see Table 1) and is additive when a mixture of agents are used together.

PHARMACOKINETICS

When inhaled agents have reached steady-state, the partial pressure within the alveoli (P_A) is in equilibrium with that in the arterial blood (P_A) and the brain (P_B). In this way, P_A gives an indirect measure of P_B . However, this steady-state is rarely achieved in the clinical setting as the process may take many hours, depending upon the agent and a range of physiological factors as below.

Ventilation

Increased alveolar ventilation results in a faster rise in P_A and therefore P_B will also rise more quickly, reducing the onset of anaesthesia time. Functional residual capacity (FRC) is also significant. A large functional residual capacity (FRC) will effectively dilute the inspired concentration and increase the onset time whereas a small FRC will allow P_A to rise rapidly.

Inspired concentration of inhalational agent

Increasing the inspired concentration of inhaled anaesthetic agent leads to a more rapid rise in P_A and so reduces onset time.

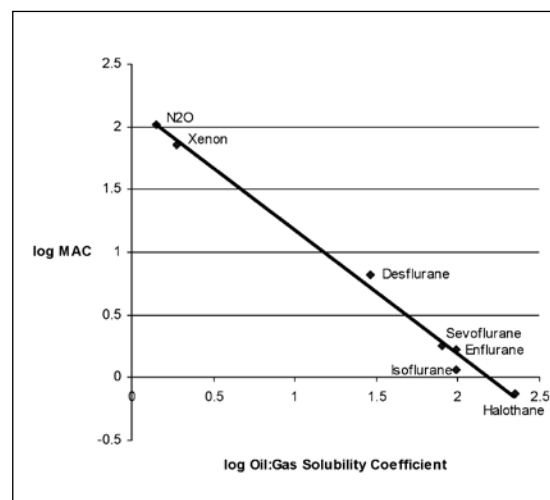


Figure 1. Relationship between MAC and oil:gas solubility coefficient

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Table 1. Factors affecting the MAC of an inhalational agent

	Effect on MAC
Physiological and metabolic factors	
Age	
Infancy and childhood	↑
Neonatal period and old age	↓
Pregnancy	↓
Hyperthermia	↑
Hypothermia	↓↓
Hyperthyroidism	↑
Hypothyroidism	↓
Hypernatraemia	↑
Pharmacological factors	
Catecholamines and sympathomimetics	↑
α ₂ agonists	↓
Sedatives	↓↓
Opioid analgesics	
acute use	↓
chronic use	↑
Alcohol	
acute intake	↓
chronic intake	↑
Amphetamines	
acute dosage	↑↑↑
chronic dosage	↓
Lithium	↓

Cardiac output

Changes in cardiac output affect pulmonary capillary transit time. During the induction of anaesthesia, a low cardiac output reduces anaesthetic uptake, but it actually accelerates the rise in P_A and therefore the onset of anaesthesia. This effect is only important when agents with a high blood:gas partition coefficient are used (see below).

Blood:gas partition coefficient

The blood:gas partition coefficient is defined as the ratio of the amount of anaesthetic in blood and gas when the two phases are of equal

volume and pressure and in equilibrium at 37°C. Intuitively it would be expected that agents with a high blood:gas partition coefficient (and therefore high solubility) would have a rapid onset. However, this is not the case as these agents will only exert a low partial pressure in blood, even when present in large amounts. The crucial factor determining onset of anaesthesia is the partial pressure of the agent in the blood (P_A) and subsequently in the brain (P_B). Therefore agents with a low blood:gas partition coefficient will exert a high partial pressure and produce a more rapid onset and offset of action.

Metabolism

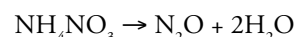
Halogen ions are released following metabolism by hepatic cytochrome p450 enzymes and have the potential to cause hepatic or renal damage. The C-F bond is relatively stable and only minimally metabolized, whereas C-Cl, C-Br and C-I bonds become progressively easier to metabolise (see Table 2).

PROPERTIES OF INDIVIDUAL INHALATIONAL ANAESTHETIC AGENTS

In this section, we will look at each agent in more detail and compare their properties. The chemical structures of the agents are diverse, and include an elemental gas (Xenon), an inorganic gas (nitrous oxide), a halogenated hydrocarbon (halothane), halogenated ethyl methyl ethers (isoflurane, enflurane, desflurane) and a polyfluorinated isopropyl methyl ether (sevoflurane) - see Figure 2. Isoflurane and enflurane are structural isomers of each other. Unlike the other volatile agents, sevoflurane is achiral. Their physiochemical properties are also diverse and are summarised in Table 3. The pharmacodynamic effects are summarised in Table 4 at the end of this section.

NITROUS OXIDE (N₂O)

N₂O has a high MAC and is widely used in combination with other inhaled anaesthetic agents or with O₂ as entonox. However, it interferes with DNA synthesis even after relatively brief exposure. It is manufactured by heating ammonium nitrate to 250°C, and impurities are removed by passage through scrubbers, water and caustic soda:



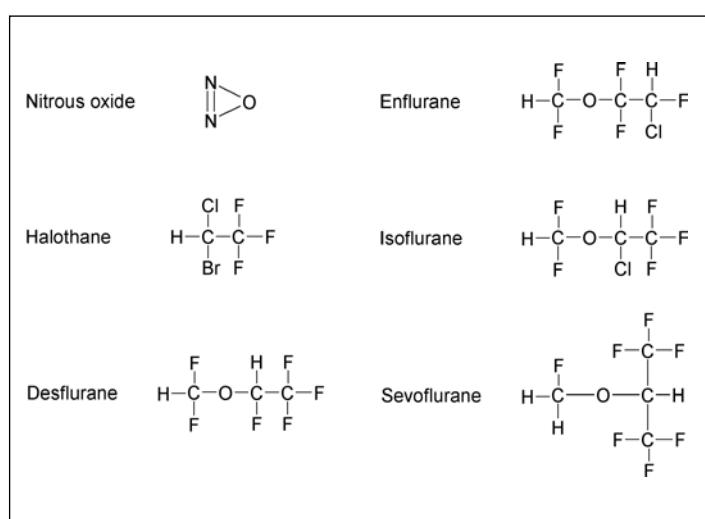
N₂O is stored as a liquid in French blue cylinders with a gauge pressure of 51 bar at 20°C. The gauge pressure does not give an indication of cylinder content until all the remaining N₂O is in the gaseous phase. The filling ratio of the cylinders (defined as the mass of N₂O in the

Table 2. Metabolism of inhaled anaesthetic agents

Agent	Percentage Metabolized	Metabolites
N ₂ O	<0.01	(N ₂)
Halothane	20	Trifluoroacetic acid, Cl ⁻ , Br ⁻
Sevoflurane	3.5	Inorganic & organic fluorides Compound A in the presence of soda lime and heat (Compounds B, C, D & E)
Enflurane	2	Inorganic & organic fluorides
Isoflurane	0.2	Trifluoroacetic acid and F ⁻
Desflurane	0.02	Trifluoroacetic acid

Table 3. *Physiochemical properties of inhaled anaesthetics*

	Halothane	Isoflurane	Enflurane	Desflurane	Sevoflurane	N₂O	Xenon
MW	197.0	184.5	184.5	168.0	200.1	44.0	131.0
BP (°C)	50.2	48.5	56.5	23.5	58.5	-88.0	-108
SVP at 20°C (kPa)	32.3	33.2	23.3	89.2	22.7	5200	
MAC (%)	0.75	1.17	1.68	6.60	1.80	105	71.0
Blood:gas partition coefficient	2.40	1.40	1.80	0.45	0.70	0.47	0.14
Oil:gas partition coefficient	224	98	98	29	80	1.4	1.9
Odour	Non-irritant, sweet	Irritant	Non-irritant	Pungent	Non-irritant	Odourless	Odourless

**Figure 2.** *Chemical structure of inhaled anaesthetics agents*

cylinder divided by the mass of water that the cylinder could hold) is 0.75 in temperate regions, but reduced to 0.67 in tropical areas to avoid cylinder explosions. It has a critical temperature of 36.5°C and its critical pressure is 72 bar (see page 131 - 'Gases and vapours').

Effects

Respiratory

- Small fall in tidal volume that is offset by an increased respiratory rate.

Cardiovascular

- Mild direct myocardial depression which is offset by an increase in sympathetic activity via its central effects.
- However, in patients with cardiac failure there may be a significant reduction in cardiac output.

Central nervous system

- Cerebral blood flow (CBF) is increased.

Concentration effect, second gas effect and diffusion hypoxia

Despite the low blood:gas solubility coefficient of N₂O, it is about 20 times more soluble than O₂ and N₂. During induction with high

concentrations of N₂O, the volume of N₂O entering the pulmonary capillaries will be significantly greater than the volume of N₂ entering the alveolus. As a consequence, the volume of the alveolus decreases, thereby increasing fractional concentrations of the remaining gases.

The concentration effect refers to the disproportionate rise in alveolar partial pressure and its high rate of approximation to the inhaled concentration. It is only seen with N₂O as it is the only agent to be present in high enough concentration and occurs due to two processes. First, the concentrating effect of the rapid N₂O uptake (as described above) and second, increased ventilation as dead space gas is drawn in to the alveolus to make up for the diminished volume.

The second gas effect is a result of the concentration effect. Volatile agents given in combination with high concentrations of N₂O will be concentrated resulting in a higher alveolar partial pressure and reduced induction time.

Diffusion hypoxia is due to the reverse of the concentration effect. At the end of anaesthesia when N₂O/O₂ is replaced with N₂/O₂, the volume of N₂O entering the alveolus from blood will be greater than the volume of N₂ entering the pulmonary capillaries resulting in dilution of all the alveolar gases including O₂. If supplemental O₂ is not given at this point, then diffusion hypoxia could result.

As well as these effects seen across the alveolar membrane, N₂O will cause a rapid expansion of any air filled spaces such as pneumothorax, vascular air embolus and luminal bowel gas.

Toxicity

N₂O oxidises the cobalt ion in vitamin B₁₂, which prevents its action as the cofactor for methionine synthase. Methionine synthase also appears to be inhibited directly by N₂O. The result is reduced synthesis of methionine, thymidine, tetrahydrofolate and DNA. Exposure of only a few hours may result in megaloblastic changes in bone marrow, and prolonged exposure may result in agranulocytosis and neurological syndromes that resemble subacute combined degeneration of the cord due to chronic vitamin B₁₂ inactivation. Teratogenicity has been shown in rats, but not convincingly demonstrated in humans, although N₂O is often avoided in the first trimester.

HALOTHANE

Halothane is unstable when exposed to light, corrodes certain metals

and dissolves into rubber. It is presented with 0.01% thymol to prevent liberation of free bromine.

Effects

Respiratory

- Minute ventilation is depressed largely due to decreased tidal volume and the normal response to hypoxia and hypercarbia are blunted.
- It has a sweet non-irritant odour and may be used for gaseous induction.
- Halothane also bronchodilates and is useful in asthmatic patients.

Cardiovascular

- Bradycardia is produced by increased vagal tone, depressed sino atrial and atrio-ventricular activity.
- It also directly depresses the myocardium and systemic vascular resistance (SVR) is reduced.
- Halothane sensitizes the heart to catecholamines which may lead to arrhythmias and the quantity of adrenaline used for infiltration should be limited.

Central nervous system

- Cerebral blood flow is increased more than any other volatile agent leading to significant increases in intra-cranial pressure (ICP). However, cerebral oxygen requirements are reduced.

Metabolism

- As much as 25% of halothane undergoes oxidative metabolism by hepatic cytochrome p450 to produce trifluoroacetic acid, Br⁻ and Cl⁻. However, when the liver becomes hypoxic, reductive metabolism predominates, producing F⁻.

Toxicity

- Hepatic damage can take one of two forms:
- Reversible form - often subclinical and is associated with a rise in hepatic transaminases. This is probably due to hepatic hypoxia.
- Fulminant hepatic necrosis ('halothane hepatitis') - trifluoroacetyl chloride may behave as a hapten which binds to hepatic proteins and induces antibody formation. Diagnosis is by exclusion, and risk factors include: multiple exposures, obesity, middle age and female sex. Mortality is around 50-75%. The incidence in adults is 1 in 2500-35000.
- Halothane should be avoided if it has been given in the previous 3 months, if there is a past history of adverse reaction to halothane, or if there is pre-existing liver disease.

ISOFLURANE

Isoflurane is widely used for maintenance of anaesthesia.

Effects

Respiratory

- Ventilation is depressed more than halothane, but less than enflurane.
- Minute ventilation is decreased, respiratory rate and PaCO₂ are increased.

- It has a pungent smell and can cause upper airway irritability and breath-holding so gaseous induction is not recommended. However it does cause some bronchodilation.

Cardiovascular

- The main effect is to reduce SVR resulting in compensatory tachycardia and only a small decrease in myocardial contractility.
- It has been proposed that isoflurane may cause 'coronary steal' whereby normally responsive coronary arterioles are dilated and divert blood away from areas supplied by diseased and unresponsive vessels, resulting in ischaemia. However, recent work suggests that if coronary perfusion is maintained, coronary steal does not occur.
- Isoflurane may also have myocardial protective properties via its effects on ATP-dependent potassium channels.

Central nervous system

- Of all the volatile agents, isoflurane produces the best balance of reduced cerebral oxygen requirement and minimal increase in CBF.

Toxicity

- Carbon monoxide may be produced by a reaction between the -CHF₂ group and dry soda lime (or baralyme). Enflurane and desflurane may also react in a similar manner.

ENFLURANE

Its use has decreased due to newer agents with more favourable profiles.

Effects

Respiratory

- Causes more depression of ventilation than the other agents with a reduction in minute volume and increase in PaCO₂. The response to hypercarbia is blunted.

Cardiovascular

- Heart rate increases, but cardiac output, contractility, systemic vascular resistance and blood pressure fall.

Central nervous system

- High concentrations of enflurane in the presence of hypocarbia produce a 3Hz spike and wave pattern on the EEG consistent with grand mal activity. It is therefore usually avoided in epileptic patients.
- There is an increase in CBF and ICP to a degree in-between halothane and isoflurane.

Metabolism

- Only 2% is metabolized by hepatic cytochrome P450. F⁻ ions are produced, but rarely reach the concentration (> 40 mcmol.l⁻¹) known to produce reversible nephropathy. Even so, it is usually avoided in patients with renal impairment.

Toxicity

- Hepatic damage may occur.

DESFLURANE

Desflurane's relatively low boiling point (23.5°C) makes it extremely volatile, however, since this temperature is close to ambient temperature in many theatre settings, full vapour saturation cannot be guaranteed if a conventional vaporizer is employed. Therefore, a Tec 6 vaporizer is used which heats the agent to 39°C at a pressure of 2 atmospheres, ensuring full vapour saturation which enables a carefully regulated amount of vapour to be added to the fresh gas flow. Its low blood:gas partition coefficient results in fast onset and offset of action. These properties make it ideal for long procedures where rapid wake-up is important to assess the patient (e.g. after neurosurgery).

Effects

Respiratory

- Similar respiratory effects to the other agents with a rise in PaCO_2 and a fall in minute ventilation. These effects are more pronounced than halothane, but less than isoflurane and enflurane.
- It has a potent odour and can cause coughing and breath holding and is not suitable for induction.

Cardiovascular

- Effects are similar to isoflurane, but in concentrations above 1 MAC, desflurane may produce tachycardia and hypertension.
- Care should be taken in patients with ischaemic heart disease. Vascular resistance falls in the cerebral and coronary circulations.

Metabolism

- Only 0.02% is metabolised.

SEVOFLURANE

Effects

Respiratory

- Ventilation is depressed in a predictable manner with a rise in PaCO_2 and a fall in minute ventilation.
- Its pleasant odour and relatively low blood:gas partition coefficient make it particularly suitable for induction.

Cardiovascular

- Heart rate and contractility are unchanged, but a fall in SVR leads to a reduction in blood pressure.
- Vascular resistance in the cerebral and coronary circulations is reduced.

Central nervous system

- There is some evidence that children exhibit a higher incidence of post operative agitation and delirium compared with halothane.

Metabolism

- Sevoflurane undergoes hepatic metabolism by cytochrome p450 (2E1) to a greater extent than all the other commonly used volatile agents apart from halothane. Hexafluoroisopropanol and inorganic

F^- are produced, although renal toxicity is not observed even when F^- plasma levels reach 50mmol.l⁻¹.

Toxicity

When sevoflurane is administered in a circle system using soda lime or baralyme, a number of compounds are produced, named compounds A-E. Only compounds A and B are present in significant quantities. Animal studies extrapolated to humans suggest a human nephrotoxic threshold of 150-200ppm but studies have shown that even with flow rates of 0.25l.min⁻¹ for 5 hours, then the level of compound A produced peaks at less than 20ppm and is not associated with renal impairment.

ETHER (Diethyl ether)

This is an inexpensive agent made from sugar cane (ethanol) that is still used in isolated settings in some countries. It is the volatile agent of choice when general anaesthesia is needed but no oxygen is available.

Effects

Respiratory

- Ether stimulates respiration and when too much ether is given respiration becomes depressed before the heart. These effects make ether a relatively 'safe' anaesthetic agent and its continued use in some isolated settings in the developing world.
- It is a bronchodilator and may be used as the sole anaesthetic agent and is capable of producing good abdominal muscle relaxation.
- It stimulates salivation and is best used with an antisialogogue premedication
- Ether is associated with a slow onset and a slow recovery. The vapour is unpleasant to breathe initially and causes irritation of the bronchial tree which may slow down the induction of anaesthesia.

Cardiovascular

- Cardiac output and blood pressure are usually increased due to its sympathomimetic effect mediated by adrenaline release.

Other effects

- Ether has analgesic properties.
- The incidence of nausea and vomiting is higher with ether than with other agents. The frequency is related to the concentration of ether used and is lower when ether is given via an endotracheal tube during relaxant anaesthesia.
- Ether causes little uterine relaxation and it is especially useful for caesarean section (because the baby tolerates it and the uterus contracts well). It is better avoided in moderate or severe pre eclampsia because of its sympathomimetic activity.

Adverse effects

Ether is explosive when mixed with oxygen and is inflammable in air. It may be ignited by a flame or an electrical spark such as those produced by diathermy or static electricity. The ether vapour is inflammable within the patient (lungs, airway or stomach full of vapour) or outside the patient within 25cm of the anaesthetic circuit. Scavenging must always be carried out (where possible) to avoid contact between heavy

inflammable ether vapour and diathermy apparatus or other electrical devices that may spark. If the end of the scavenging tube is placed on the floor (away from any possible sources of ignition) then the heavy ether vapour will remain at floor level and the smell of the agent to the surgical and anaesthetic team reduced.

XENON

Xenon (Xe) is an inert, odourless gas that is present in minute quantities in the atmosphere and is produced by the fractional distillation of air. It has a high MAC and very low blood:gas partition coefficient resulting in a faster onset and offset of action than desflurane or N₂O. It also has

significant analgesic properties and is not metabolised. The high cost of manufacture has limited its use to mainly that of a research agent.

FURTHER READING

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Table 4. Effects of inhaled anaesthetics

	Halothane	Isoflurane	Enflurane	Desflurane	Sevoflurane
Cardiovascular effects:					
Contractility	↓↓↓	↓	↓↓	minimal	↓
Heart rate	↓↓	↑↑	↑	↑↑	nil
Systemic vascular resistance	↓	↓↓	↓	↓↓	↓
Blood pressure	↓↓	↓↓	↓↓	↓↓	↓
Coronary steal	no	possibly	no	no	no
Splanchnic blood flow	↓	unchanged	↓	unchanged	unchanged
Sensitization to catecholamines	↑↑↑	nil	↑	nil	nil
Respiratory effects:					
Respiratory rate	↑	↑↑	↑↑	↑↑	↑↑
Tidal volume	↓	↓↓	↓↓↓	↓↓	↓
PaCO ₂	unchanged	↑↑	↑↑↑	↑↑	↑
Other effects:					
Cerebral blood flow	↑↑↑	↑	↑	↑	↑
Cerebral O ₂ requirement	↓	↓	↓	↓	↓
EEG	burst suppression	burst suppression	epileptiform activity	burst suppression	burst suppression
Effect on uterus	some relaxation	some relaxation	some relaxation	some relaxation	some relaxation
Potential of muscle relaxation	some	significant	significant	significant	significant
Analgesia	some	some	some	some	some

Originally published in *Anaesthesia Tutorial of the Week* (2007)

Pharmacology of Neuromuscular Blocking Drugs and Anticholinesterases

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Summary

Neuromuscular blocking drugs (NMBDs) are quaternary ammonium compounds structurally similar to acetylcholine (ACh); they act mostly at the post-junctional nicotinic receptor of the neuromuscular junction. NMBDs may be agonists ('depolarising' NMBDs) or antagonists ('non-depolarizing' NMBDs) at the nicotinic receptor. Anticholinesterase drugs (also known as acetylcholinesterase inhibitors) are used to reverse the effects of non-depolarizing NMBDs. These drugs increase the concentration of ACh at the neuromuscular junction by inhibiting the enzyme acetylcholinesterase.

INTRODUCTION

Neuromuscular blocking drugs (NMBDs) are used in anaesthesia to impair neuromuscular transmission and provide skeletal muscle relaxation. These drugs enable the anaesthetist to perform tracheal intubation, facilitate ventilation and to provide optimal surgical operating conditions, for example during laparotomy.

DEPOLARIZING NMBDs - SUXAMETHONIUM

Suxamethonium (succinylcholine) is the only depolarizing NMBD in clinical use. Structurally it is two ACh molecules joined together and it acts as an agonist at the nicotinic receptor. Suxamethonium binds with the two alpha sub-units of the receptor mimicking ACh resulting in membrane depolarization. When depolarization occurs it causes muscle contraction, which occurs rapidly and is observed clinically as muscle fasciculation. After depolarization the membrane potential must be reset before further depolarization can occur and skeletal muscle remains in a state of flaccid relaxation until this occurs.

An intravenous dose of suxamethonium of 1.0-1.5mg.kg⁻¹ produces profound neuromuscular block within 60 seconds, this is faster than with any other NMBD. The blockade typically resolves spontaneously after approximately 10 minutes. Suxamethonium results in a phase I block, characterised by absence of fade and post-tetanic facilitation on peripheral nerve stimulation. Suxamethonium is hydrolysed rapidly by plasma cholinesterase to succinyl monocholine and choline. Prior to use it is stored at 4°C to prevent hydrolysis.

Although not commonly used, an infusion of suxamethonium can be used to produce prolonged neuromuscular blockade. 500mg of suxamethonium are put in a 500ml bag of saline (0.1% solution). The rate of infusion is adjusted to achieve the desired degree of relaxation, usually 5-15mg.kg⁻¹.h⁻¹ (5-15ml.kg⁻¹.h⁻¹). Pre-treatment with atropine is required if this technique is used.

Suxamethonium can be given intramuscularly at a dose of 3-5mg.kg⁻¹. The onset is considerably slower than when given intravenously. This route is usually used only in infants where venous access is not possible.

Indications and side effects

Suxamethonium has the most rapid and predictable onset of action of all the NMBDs. It also has a short duration of action, with recovery commencing at about 4 minutes and complete by about 10 minutes. This means that it is the drug of choice for anaesthesia when rapid tracheal intubation is required, for example in an emergency situation, or when a rapid sequence induction (RSI) is indicated in patients at risk of aspiration. It is also indicated when rapid recovery of neuromuscular function may be required.

Suxamethonium has several side effects:

Bradycardia

- Occurs due to stimulation of muscarinic receptors in the sino-atrial node.
- Bradycardia is more common in children and after repeated doses of the drug.
- Increased intra-ocular pressure.
- There is a theoretical risk of expulsion of vitreal contents with the use of suxamethonium in patients with a penetrating eye injury.
- This risk must be balanced with the risk of aspiration of gastric contents in emergency surgery.

Muscle pain

- Occurs commonly, especially in young, fit adults with early ambulation.
- Strategies such as precurarization exist to reduce the incidence but no strategy is fully preventative. This is where a small dose of a non-depolarising NMBD is given at least three minutes before suxamethonium, but is not recommended for routine use.

Hyperkalaemia

- Average serum potassium levels increase by 0.5mmol.l⁻¹ on administration of suxamethonium. Patients with pre-existing hyperkalaemia are at risk of cardiac arrhythmias and death.
- Life threatening hyperkalaemia can occur in patients with burns, muscular dystrophies, and

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spinal cord injuries. This may be due to proliferation of extra junctional receptors in these patients. Maximal risk of hyperkalaemia in burn patients occurs during days 9-60 after the burn.

- The use of suxamethonium within the first 2-3 days after a severe burn injury is regarded as safe.

Increased intragastric pressure

- The rise in intragastric pressure following administration of suxamethonium is counteracted by a concomitant elevation in the lower oesophageal sphincter pressure.

Phase II block

- This phenomenon may occur after large or repeated doses of suxamethonium.
- Neuromuscular block is prolonged and peripheral nerve stimulation results in fade of the train-of-four twitch height response and post tetanic facilitation.

Anaphylaxis

- Suxamethonium is responsible for over 50% of anaphylactic reactions to NMBDs.
- Prolonged block due to reduced plasma cholinesterase activity
- This may be due to inherited or acquired causes.
- Inherited causes of prolonged block after suxamethonium occur due to production of atypical plasma cholinesterase. The structure of the cholinesterase enzyme is determined genetically by a gene on chromosome 3, this gene is described as the usual gene (94% of the population homozygotes). Several variants from the usual gene exist - the three commonest are known as the atypical, silent and fluoride resistant genes. Individuals with variant genes have atypical cholinesterase enzyme, and develop prolonged neuromuscular block after suxamethonium. Duration of prolonged block varies from 30 minutes (e.g. people heterozygous for the atypical gene) to several hours (e.g. homozygotes for the silent gene.)
- Acquired causes include reduced enzyme synthesis, which may occur in liver disease, carcinomatosis, pregnancy or starvation (hypoproteinaemic states), cardiac failure, renal failure, and burns. The co-administration of other drugs such as etomidate, ester local anaesthetics, methotrexate, remifentanyl and esmolol can result in a reduction in plasma cholinesterase activity.

Malignant hyperthermia

- This condition may be triggered by suxamethonium and therefore its use is absolutely contraindicated in susceptible patients.

NON-DEPOLARIZING NMBDs

Non-depolarizing drugs are competitive antagonists of ACh at the postsynaptic nicotinic receptor. They bind to one or both α -subunits of the receptor and prevent depolarization due to ACh. The binding of antagonists to the receptor is reversible and repeated association and dissociation occurs. Neuromuscular blockade starts to occur when 70-80% of receptors are antagonised, to produce a complete block over 90% of receptors must be occupied.

Non-depolarizing NMBDs are also believed to have an action at pre-junctional receptors at the neuromuscular junction. Stimulation of pre-junctional receptors by ACh normally results in further mobilisation of ACh to cope with increasing stimulation frequency. Non-depolarizing NMBDs antagonise these receptors and inhibit this process.

When assessing the block caused by non-depolarizing NMBDs with a peripheral nerve stimulator a characteristic response is observed. Fade of twitch height response occurs during a train of four or tetanic pattern of stimulation. Fade is due to the action of these drugs at the presynaptic receptor resulting in reduced availability of ACh with repeated nerve stimulation. Post tetanic facilitation of neuromuscular transmission is another feature of non-depolarizing neuromuscular blockade and is due to increased quantities of ACh in the synapse of the junction after tetanic stimulation.

Non-depolarizing NMBDs are not metabolised at the neuromuscular junction and resolution of block is due to a dilutional effect of the drug with time. They are highly ionised, water-soluble drugs and their volume of distribution approximates to that of plasma and extracellular fluid. There are two groups of non-depolarizing NMBDs, benzyliisoquinolinium compounds and aminosteroid compounds.

Benzyliisoquinolinium compounds

These drugs consist of two quaternary ammonium groups joined by a chain of methyl groups. They are more liable to break down in the plasma and often cause release of histamine; examples include tubocurarine, atracurium, cisatracurium and mivacurium.

Tubocurarine

- A drug with a long onset and prolonged duration of action (see Table 1). It causes marked histamine release, with hypotension and tachycardia.
- Ganglion blockade may occur with large doses.
- Tubocurarine is excreted unchanged mostly in the urine but also in bile. Its effects are prolonged in renal failure. It has been superseded by agents with better side effect profiles and is no longer available in the UK.

Atracurium

- A racemic mixture of 10 stereoisomers and geometric isomers. Atracurium has an intermediate onset and duration of action. It causes release of histamine but has no direct cardiovascular effects.
- Metabolism is by Hofmann degradation and ester hydrolysis in the plasma, hence its duration of action is independent of renal and hepatic function.

Cisatracurium

- The R-cis R'-cis isomer of atracurium. It constitutes 15% of the parent compound and is four times more potent with a longer duration of action.
- Unlike atracurium it does not release histamine. It is metabolised by Hofmann degradation and does not accumulate in renal failure.

Mivacurium

- Mivacurium is a drug with a short duration of action of

approximately 15 minutes, making it potentially useful for short procedures. It is a racemic mixture of three isomers that is hydrolysed by plasma cholinesterase.

- Mivacurium is associated with histamine release causing significant hypotension with doses greater than 0.2mg.kg^{-1} .
- Like suxamethonium its duration of action is increased in patients with atypical plasma cholinesterase.

Aminosteroid compounds

- All aminosteroid NMBDs possess at least one quaternary ammonium group attached to a steroid nucleus. They tend not to cause histamine release and most are metabolised in an end organ before excretion.

Pancuronium

- The first steroid NMBD in clinical use has a slow onset and long duration of action.
- It does not cause histamine release but has weak sympathomimetic properties and causes tachycardia.
- It is partly de-acylated in the liver to a metabolite with neuromuscular blocking properties, and partly excreted unchanged in the urine. Its action is prolonged in renal and hepatic impairment.

Vecuronium

- Vecuronium is structurally similar to pancuronium but has a slightly faster onset and shorter (intermediate) duration of action. It does not release histamine or have any cardiovascular effects.
- Metabolism in the liver occurs to active metabolites before being excreted in the bile and urine.
- Vecuronium is unstable in solution and is stored as powder and requires mixing with water prior to administration.

Rocuronium

- This monoquaternary amine has the most rapid onset of the clinically available non-depolarizing NMBDs.
- Intubating conditions can be achieved in 60-90 seconds after

an induction dose of 0.6mg/kg . Rocuronium has an intermediate duration of action and is metabolised in the liver and excreted in the bile.

- Rocuronium has minimal cardiovascular effects and does not release histamine, however, it has a higher incidence of anaphylactic reactions than other aminosteroid NMBDs.

ANTICHOLINESTERASES

Anticholinesterases (also known as acetylcholinesterase inhibitors) are agents that inhibit the action of the acetylcholinesterase enzyme at the neuromuscular junction. Enzyme inhibition leads to a reduction in the breakdown of ACh and potentiates its action.

Anticholinesterases are used in anaesthesia to reverse the effects of non-depolarizing NMBDs. Reversal of non-depolarizing neuromuscular blockade usually occurs at the end of surgery, and should not take place before some resolution of the block has already occurred. Early administration of anticholinesterase may be ineffective due to high receptor occupancy by the NMBD. Reversal of intermediate acting NMBDs with anticholinesterase should be at least 20 minutes after giving the drug. If peripheral nerve stimulation is used, at least 2 twitches on a train of four should be detected before attempting reversal. The most reliable sign that a block is fully reversed by anticholinesterase is a sustained response to tetanic stimulation with a peripheral nerve stimulator (i.e. no fade). However tetanic stimulation can be painful to apply in awake individuals. Clinical tests of adequate resolution of neuromuscular block include the ability to lift the head from the bed for 5 seconds, although this is a much less reliable assessment.

Anticholinesterases will augment the Phase I block due to depolarizing NMBDs and there is no role for anticholinesterases in reversing the effects of suxamethonium.

Side effects of anticholinesterase agents

Anticholinesterases cause a build up of ACh that results in potentiation of its effects at muscarinic receptors. This can cause bradycardia, miosis, GI upset, nausea, bronchospasm, increased bronchial secretions, sweating and salivation. For this reason an antimuscarinic such as glycopyrronium or atropine must be administered along with the anticholinesterase to minimise these effects.

Table 1. Dose, speed of onset and duration of neuromuscular blocking drugs

Drug	Dose (mg.g^{-1})	Onset time (min)	Duration (min)
Succinylcholine	1.0-1.5	< 1	5-10
Tubocurarine	0.5	3-5	30-50
Atracurium	0.5	2-3	20-30
Cisatracurium	0.1	2-3	30-40
Mivacurium	0.15-0.20	2-3	10-20
Pancuronium	0.1	3-5	40-60
Vecuronium	0.1	2-3	20-30
Rocuronium	0.6	1-2	30-40

Anticholinesterase drugs

Neostigmine

- The most commonly used anticholinesterase in anaesthesia is neostigmine. This is a water-soluble quaternary ammonium compound that combines reversibly with the esteratic site of the acetylcholinesterase enzyme rendering it inactive for about 30 minutes.
- Neostigmine is given as an intravenous injection at a dose of 0.05mg.kg^{-1} (maximum 5mg), and should be administered with glycopyrronium 0.01mg.kg^{-1} or atropine 0.02mg.kg^{-1} . Neostigmine starts to take effect after approximately 2 minutes but has its maximal effect at 5-7 minutes. It is excreted unchanged by the kidney and has a half-life of about 45 minutes.

Edrophonium

- This anticholinesterase forms an ionic bond at the anionic site of the enzyme. Bonding is reversible and short lived in the order of a few minutes.
- Edrophonium is used as a diagnostic test for myasthenia gravis. ACh potentiation by the drug results in a transient increase in muscle power in the patients with this autoimmune disease.
- Edrophonium is rarely used to reverse the effects of NMBDs as its effects are short lived and neuromuscular block may increase after an initial recovery.

Pyridostigmine

- This agent has a longer onset than neostigmine and lasts for several hours. It is used more frequently as a therapy for myasthenia gravis.

Physostigmine

- Like neostigmine and pyridostigmine, physostigmine acts reversibly at the esteratic site of the acetylcholinesterase enzyme.
- As it is more lipid soluble than the other agents it can be absorbed from the GI tract and crosses the blood brain barrier.

Organophosphorous compounds

- These substances are found in some pesticides and agents used in chemical warfare.
- Organophosphorous compounds form an irreversible bond with the enzyme and recovery only occurs after generation of new enzyme, which takes weeks. Poisoning results in salivation, sweating, bradycardia, bronchospasm and muscle weakness.
- Treatment is with atropine and supportive measures.

OTHER "REVERSAL" DRUGS

Sugammadex is a novel drug designed to antagonize the effects of aminosteroid NMBDs, particularly rocuronium. It is a cyclodextrin molecule, and rapidly reverses the effects of NMBDs by encapsulation.

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Originally published in *Update in Anaesthesia*, edition 23 (2007)

Paracetamol - A Review of Three Routes of Administration

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Summary

The disproportionate cost, slow onset time and wide variation in bioavailability make rectal paracetamol less attractive in the presence of the intravenous formulation.

Given the similar cost, intravenous paracetamol should be considered as a more effective alternative to suppositories, when oral dosing is not possible. It may also have a role to play when prompt analgesia is required and oral administration is not appropriate. Oral paracetamol is a simple well-tolerated analgesic; however a more generous loading dose is needed if meaningful early plasma concentrations are to be achieved. Intravenous paracetamol provides a method of achieving rapid therapeutic concentrations of paracetamol that can subsequently be maintained by oral absorption.

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MECHANISM OF ACTION

Although paracetamol was found to be an effective analgesic more than a century ago, its mechanism of action remains unclear and is the subject of continuing research. Unlike non-steroidal anti-inflammatory drugs (NSAIDs), whose analgesic and anti-inflammatory effects are thought to relate to their inhibition of the cyclooxygenase enzymes (COX-1 and COX-2), paracetamol is a weak anti-inflammatory agent with an absence of COX-related adverse effects. Experimental studies show that paracetamol can inhibit both COX-1 and COX-2 in an environment where the ambient concentrations of arachidonic acid and peroxides are kept low. However, where extracellular concentrations of these two chemicals are high in inflammatory conditions such as rheumatoid arthritis, paracetamol shows limited in vivo suppression of inflammation and platelet activity.¹

It has been demonstrated that paracetamol may exert its analgesic effect via molecular targets distinct from COX. In the brain and spinal cord paracetamol is conjugated with arachidonic acid to form N-arachidonoylphenolamine (AM404).² AM404 is a known activator of the capsaicin receptor (TRPV1) and the cannabinoid CB1 receptor system both of which confer analgesia in the central nervous system. This pathway may also account for the antipyretic effect of paracetamol, known to be related to inhibition of prostaglandin production in the brain.³ Cerebrospinal fluid levels of prostaglandin are shown to be high in rats during pyrogen induced fever, and these levels are reduced along with the fever after paracetamol administration.⁴ At this time, however, such a link remains speculative.

ANALGESIC EFFICACY

There is good evidence to show paracetamol as an analgesic is effective and safe. A Cochrane systematic review of oral paracetamol use in acute postoperative pain analysing 47 studies, including 4186 patients, found the number-needed-to-treat (NNT) - see box - for at least 50% pain relief, over 4-6 hours was 3.8 (95% confidence intervals: 3.4-4.4).⁵ There was no significant difference in the frequency of reported adverse effects between paracetamol and placebo.

Side-effects after paracetamol use are rare, and usually mild and transient. At therapeutic doses paracetamol use is associated with an extremely low rate of liver dysfunction (less than 1 in 500000)⁶ and there are only two contra-indications; paracetamol hypersensitivity and severe hepatocellular insufficiency. There are few known drug interactions and breast-feeding women may use paracetamol. Paracetamol has been shown to have a comparable benefit to ibuprofen and diclofenac in general and orthopaedic surgery⁷ and can significantly reduce the opiate requirement postoperatively – it has an **opioid-sparing effect**.⁸

Number-needed-to-treat (NNT) – This gives the clinician an indication of the size of the treatment effect described by a clinical trial of a treatment. It tells the reader the number of patients that they would need to treat in order to see an effect in one patient.

95% confidence intervals – These give the reader of a study an indication of the reliability of the result of the study. If you repeated the study 100 times, 95 of the studies would give a result within these two confidence intervals. Larger studies tend to give narrower confidence intervals (i.e. results that more accurately represent reality). 95% (rather than a higher or lower figure) is a generally agreed acceptable level of certainty that a study result reflects a true treatment effect.

A **placebo** is a pharmacologically inert substance that may have a medical effect based solely on the power of suggestion. This is known as the placebo effect. By comparing drugs to a placebo, the pharmacological effects of the study drug are identified.

ROUTE OF ADMINISTRATION

Plasma concentrations of paracetamol between 10-20mcg.ml⁻¹ are known to produce an antipyretic effect but the concentrations required to provide analgesia are not well defined.⁹ One study, in which 120 children were given oral or rectal paracetamol post tonsillectomy, concluded an effect site concentration of 10mcg.ml⁻¹ was needed to achieve pain scores of less than 4/10.¹⁰ However, both higher and lower values than this have been suggested.^{11,12} There are significant differences in the absorption of paracetamol, and therefore in the

time to reach peak plasma levels, when it is given orally, rectally or intravenously. All three routes are able to achieve adequate plasma concentrations, but intravenous (IV) administration can achieve these levels in a shorter time.

Oral administration

Paracetamol is well absorbed from the gastrointestinal tract with low first pass metabolism in the liver, and oral bioavailability is estimated at 63-89%. Two recent trials have compared the administration of oral and intravenous paracetamol. In a study of 35 patients undergoing day-surgery, intravenous propacetamol (the IV prodrug of paracetamol) reached therapeutic plasma concentrations more quickly and predictably than oral paracetamol.¹¹

Paracetamol plasma concentrations were observed for the first 80 minutes after administration of either 1g or 2g oral paracetamol or 2g intravenous propacetamol. Intravenous paracetamol provided an average concentration within the therapeutic range after 20 minutes. There was a large and unpredictable variability with oral administration; some patients who received 1g orally did not achieve detectable plasma levels within the 80 minute study period, and the average plasma concentration after receiving this dose was subtherapeutic throughout. 2g oral paracetamol achieved a median plasma concentration within the therapeutic range after 40 minutes, suggesting that when paracetamol is given orally, a loading dose can reduce the time needed to achieve therapeutic levels.

Clinically, this difference has been shown to lead to a faster onset of analgesia when paracetamol is given intravenously. Propacetamol infusion provided a significantly faster onset of analgesia than oral paracetamol, after 3rd molar surgery.¹³ Intravenous propacetamol had a greatly reduced time until meaningful pain relief (8 minutes for propacetamol compared to 37 minutes for oral paracetamol) and maximal pain relief (15 minutes for propacetamol compared to 1 hour for oral paracetamol).

First Pass Metabolism – A drug taken orally is absorbed through the intestine wall into the portal vein system and then delivered to the liver. It may therefore be partially metabolised in the liver before reaching its target site. Drugs given sublingually, intramuscularly or intravenously avoid first pass metabolism.

Oral Bioavailability – The fraction of an oral dose of a drug that reaches the systemic circulation, compared to the same dose given intravenously. Drugs given intravenously have 100% bioavailability.

A **prodrug** is the inactive form of a drug that is broken down by a body enzyme into its active form. This can provide a way of administering drugs that would otherwise be toxic if given systemically in the active form.

Rectal administration

Rectal absorption of paracetamol is more unpredictable, with bioavailability between 24-98%. The variability in the rate and extent of absorption of suppositories is thought to be due to several factors. Regarding the formulation of the suppositories, lipophilic bases provide greater bioavailability than hydrophilic bases, and absorption is affected by the volume of the suppository, the number of suppositories used, and the particle size of the paracetamol.¹⁴ Rectal pH may also influence the absorption of paracetamol, altering the

degree of dissociation and therefore the ability of the drug to pass through biological membranes. In children, rectal pH can vary from 7.8-11.4, and in this range the degree of dissociation of paracetamol will vary from 2-99%.¹⁵

Several studies have shown that the time needed to achieve therapeutic plasma levels with rectal administration is significantly greater than with the oral or intravenous routes. In healthy adult volunteers given doses of 15mg.kg⁻¹, 25mg.kg⁻¹, 35mg.kg⁻¹ and 45mg.kg⁻¹, only doses of 35mg.kg⁻¹ and 45mg.kg⁻¹ provided concentrations above the minimum therapeutic level of 10mcg.ml⁻¹ for a significant period of time (median 5.5 and 6 hours respectively).¹⁶ A minimum duration of 1-2 hours was needed before this level was achieved. 15mg.kg⁻¹ failed to achieve a median plasma concentration above 10mcg.ml⁻¹ at any time, while 25mg.kg⁻¹ achieved plasma concentrations at the lower end of the therapeutic range. A higher loading dose (45mg.kg⁻¹) was not associated with a significantly greater risk of overdose, as the highest plasma concentration measured in the study was 25mcg.ml⁻¹, substantially less than the accepted toxic concentration of 120mcg.ml⁻¹.

A study of the pharmacokinetics of paracetamol, after repeated rectal administration of 25mg.kg⁻¹, 6 hourly, in 23 children following major surgery showed large variations in the absorption and resulting steady state concentrations.¹⁵ The mean time to reach 90% of the steady state concentration was 11.4 hours.

In a randomised study of 48 patients admitted to ICU after cardiac surgery,¹⁷ half received paracetamol as suppositories and half received intravenous injections. Mean plasma concentration peaked at 14.4mcg.ml⁻¹ within 20 minutes after intravenous administration of 1g, while after a 1g suppository, the mean plasma concentration at 80 minutes was 1.2mcg.ml⁻¹. Stable plasma concentrations within the therapeutic range were not reached until after the 3rd rectal dose. Similarly, a study of oral and rectal paracetamol in 24 women following minor gynaecological laparoscopic surgery found that after the administration of 2g rectally, the mean plasma concentration at 4 hours was below the minimum analgesic level (8.4mcg.ml⁻¹, range 4.2-16.3).¹⁸

There is some evidence to show that the delay in reaching therapeutic plasma levels may limit the usefulness of rectal paracetamol as analgesia in the immediate postoperative period. Hein et al performed a randomised controlled, double-blinded trial involving 140 women undergoing elective termination of pregnancy.¹⁹ Following surgery, patients were randomly allocated to receive either 1g paracetamol rectally, or a placebo suppository. There was no difference in postoperative pain scores between the 2 groups, and no difference in the need for additional analgesia or for time to discharge.

Intravenous administration

As well as being available for oral and rectal administration, paracetamol has previously been available for intravenous use in the form of its pro-drug, propacetamol. Used in France since 1985, propacetamol, provided as a powder for reconstitution, is water soluble and rapidly hydrolysed by plasma esterases to form paracetamol and diethylglycine; a dose of 1g propacetamol provides 0.5g paracetamol after hydrolysis.

The analgesic benefit of propacetamol is well recognised. In a double-

blinded study of analgesia following gynaecological surgery, 200 women were randomised to receive either 2 intravenous doses of propacetamol 2g, or ketorolac 30mg, alongside morphine via a patient-controlled analgesia (PCA) system.²⁰ Patients were monitored for 12 hours and propacetamol was found to be comparable to ketorolac in terms of pain scores and reduction in morphine consumption. In a study of patients undergoing dental extraction, propacetamol was significantly better than placebo for all measured parameters; pain relief, pain intensity, patient's global evaluation and duration of analgesia.¹³ Similarly propacetamol and diclofenac were found to be similarly effective and superior to placebo following total hip arthroplasty.²¹ Although an effective analgesic, propacetamol has a relatively high incidence of adverse effects (up to 49% of patients will develop local pain at the injection site²²) and there have been reports of contact dermatitis in health-care workers administering the drug.

Intravenous paracetamol (Perfalgan, Bristol-Myers Squibb) is formulated as a 10mg.ml⁻¹ aqueous solution in 50ml and 100ml glass vials, for infusion over 15 minutes. Solubility is achieved through addition of the hydrophilic ingredients mannitol and disodium phosphate, while hydrolysis to 4-aminophenol, a toxic nitrogenous compound, is avoided by the addition of buffers to sustain neutral pH. Containment in glass vials prevents oxidation. Advantages of intravenous paracetamol over propacetamol are that it is available in a preformed solution, and it is not associated with pain on injection or contact dermatitis. Paracetamol is bioequivalent to propacetamol.²³

A number of trials have shown comparable efficacy between intravenous paracetamol and propacetamol. Recently, two randomised, double-blinded placebo controlled trials of paracetamol analgesia, after major orthopaedic surgery and dental surgery, found no difference between intravenous paracetamol and propacetamol.^{6,22} Both interventions were significantly superior to placebo for pain relief, time to morphine rescue, and overall morphine sparing. Both studies showed intravenous paracetamol to have a rate of adverse effects almost identical to that of placebo, and no cases of injection site reaction were reported.

Patient Controlled Analgesia – An infusion pump filled with an opiate is connected to the patient via an intravenous drip. The pump can deliver a pre-set dose of analgesic on demand when the patient presses the PCA button. A lockout time is set when the pump is started, and during this period no further doses are given. This prevents the patient inadvertently overdosing.

Bioequivalence describes pharmaceutical compounds that are equal to each other in bioavailability and potency.

COST²⁴

Route of administration	Cost per 1g dose
Oral	£0.02
Intravenous	£1.50
Rectal	£1.98

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Non-steroidal Anti-inflammatory Drugs

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Summary

NSAIDs are effective analgesics used almost universally to reduce perioperative and long term pain, especially when associated with inflammatory conditions. The side effects however, are numerous and clinically important, possibly having far greater impact than we imagine. The future may herald tighter regulation of this class of drug.

INTRODUCTION

The description “non-steroidal anti-inflammatory drugs” (NSAIDs) is the term used when referring to a group of drugs that are united by their mode of action (anti-inflammatory) and by virtue of not being steroids. Most are organic acids and conventional NSAIDs can be grouped according to their chemical structure (Table 1). Apart from their anti-inflammatory action, they also have antipyretic and analgesic activity. The latter is particularly useful as this comes without any sedation, effect on respiration in therapeutic doses or the potential for addiction, all normally associated with opioid drugs. Most common NSAIDs can be given orally or rectally and some may be administered intravenously. Most NSAIDs display similarities in their side effect profile.

MECHANISM OF ACTION

Conventional NSAIDs act as non-specific inhibitors of the enzyme cyclo-oxygenase (COX), which is part of the arachidonic acid pathway that leads to the formation of various eicosanoid messenger molecules. Therefore in addition to reducing the synthesis of prostaglandins (PGH₂, PGE₂, PGF₂), the production of leukotrienes, prostacyclins and thromboxanes are also reduced (Figure 1). Prostaglandins (PGs) act locally producing many diverse effects via G-protein coupled membrane receptors and are synthesised in most cells of the body.

The COX enzyme has two distinct isoforms termed COX-1 and COX-2. These two enzymes are coded for by two genes and expressed differentially in various tissues. The COX-1 enzyme is described as

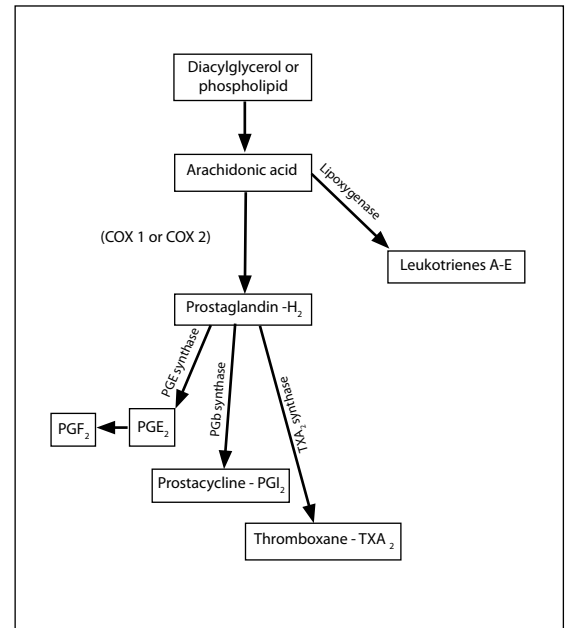


Figure 1. The prostaglandin pathway

being “constitutive” and is expressed continuously in many tissues, for example kidneys, stomach, lung liver and platelets. It is involved in various protective homeostatic mechanisms, for example renal blood flow, gastric mucosal integrity and platelet aggregation. In contrast, the COX-2 enzyme is described as being “inducible”, such that it is not normally present in any appreciable quantity in tissues and its production is induced in sites of inflammation and tissue injury by cytokines (e.g. interleukin-1) and tumour necrosis factor alpha. Conventional NSAIDs inhibit both enzymes; inhibition of COX-1 accounting for most of

Table 1. Classification of NSAIDs

Conventional NSAIDs – with examples

Salicylic acid derivatives	Aspirin
Acetic acid derivatives	Diclofenac, Indomethacin
Propionic acid derivatives	Ibuprofen, Naproxen, Ketoprofen
Enolic acid derivatives	Piroxicam, Phenylbutazone
Fenamic acid derivatives	Mefenamic acid
Non-acidic	Nabumetone

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the unwanted side effects of NSAIDs (see below) and inhibition of COX-2 accounting for the therapeutic effects. In theory the 'perfect' NSAID would therefore only inhibit COX-2, leaving COX-1 to continue with normal homeostatic processes. This ideal has recently been achieved to a degree with the introduction of specific COX-2 inhibitors. Currently available drugs in this class are celecoxib, etoricoxib and parecoxib. Rofecoxib (Vioxx) has been withdrawn by the manufacturer because of concerns about the apparent increased risk of adverse cardiovascular events (see below).

This model is an over simplification, with COX-2 probably having a greater role in other physiological processes than previously thought, particularly in female reproduction.

As shown above, the COX enzymes are involved in the production of PGH_2 , a precursor of various other PGs that play an important role in the inflammatory process. PGs themselves play little part in the direct production of pain; they cause localised increased blood flow and vascular permeability that leads to swelling and erythema seen at the site of inflammation, while PGE_2 and $\text{PGF}_2\alpha$ sensitize peripheral nerve fibres to both mechanical, chemical, thermal stimuli and locally released pain-producing stimuli such as bradykinin, histamine and serotonin. PGs are also released in the CNS where they are thought to be involved in the release of substance-P. This enhances synaptic transmission in the dorsal horns resulting in the hyperalgesia associated with inflammation. Traditionally, NSAIDs were thought to decrease pain by blocking the peripheral effects, but it is now believed that they exert at least part of their effect centrally, by reducing prostaglandin levels in the CNS.

Not surprisingly, NSAIDs have been shown to be effective analgesics drugs, particularly against bone pain (e.g. arthritis, fractures) and have a morphine-sparing effect after abdominal,¹ thoracic² and orthopaedic surgery.³ As a consequence patients experience less sedation, improved respiratory function, reduced risk of urinary retention and earlier return to eating and drinking. As a result patients mobilise sooner, and hospital costs are reduced. Consequently, these drugs have found an increasing use in the perioperative phase, in particular ketorolac (non-specific COX inhibitor) and parecoxib (COX-2 inhibitor) as they can be given parenterally.

The other therapeutic role of NSAIDs is the reduction of fever. Body temperature is normally regulated around a set-point by the hypothalamus. Prostaglandins produced in disease states, cause this set-point to be raised, an effect partly negated by NSAIDs.

SIDE EFFECTS

Gastrointestinal tract

The effects of NSAIDs on the gastric mucosa are perhaps the best recognised. Prostaglandins have a 'gastro-protective effect' in that they act to cause a decrease in gastric acid production, an increase in production of the protective gastric mucosal barrier and an increase in local gastric mucosal blood flow. Decreasing prostaglandin production therefore results in damage to the gastric mucosa. NSAIDs may also cause damage to the gastric mucosa by a direct contact physiochemical effect. A combination of both effects can lead to effects ranging from mild epigastric discomfort to gastric erosions associated with upper GI bleeding. There is considerable inter-patient variability in the degree

of sensitivity with the elderly being most at risk. COX-2 selective NSAIDs have been shown to be associated with a lower incidence of upper GI side effects.⁴

Platelets and the cardiovascular system

Impaired platelet function (reduced aggregation) is a common effect of all non-selective NSAIDs, as a result of decreased thromboxane A_2 (TXA_2) production. TXA_2 is present in large amounts in activated platelets and acts locally as a chemo-attractant for other platelets, leads to the formation of a platelet plug and induces localised vasoconstriction. Most NSAIDs inhibit COX-1 in a competitive manner and therefore is dependant on the drug concentration in the plasma. Aspirin, however, acts in a non-competitive manner by irreversibly inactivating COX. Platelets cannot synthesise proteins *de novo*, and are therefore unable to produce "new" COX enzyme, thereby rendering them ineffective for their lifespan of up to ten days. It is for this reason that aspirin must be discontinued for a week prior to elective surgery.

The cardiovascular side effects of NSAID-induced eicosanoid depletion are not simple. PGI_2 , produced by normal endothelium, is an inhibitor of platelet aggregation and contributes to the antithrombotic properties of intact blood vessels. Also, in contrast to TXA_2 , prostaglandins generally cause vasodilatation of vascular beds and increased blood flow to organs (the exception being the pulmonary vasculature where they cause vasoconstriction). Vascular PGI_2 is COX-2 dependent which might explain the higher risk of cardiovascular side effects seen with some COX-2 selective NSAIDs.

There is new evidence that the use of NSAIDs may lead to an increase in the risk of myocardial infarction (MI) in the general population.⁵ This appears to be an effect of most NSAIDs rather than being attributable to certain drugs. A small increase in MI risk is associated with the long-term use of certain NSAIDs (e.g. diclofenac), others confer no apparent increased risk (ibuprofen) or perhaps even slightly reduce the risk (Naproxen).⁶ The greatest risk appears to be with the long-term use of COX-2 inhibitors, this has been shown to be associated with an increased risk of myocardial infarction and stroke (CVA). As a result, rofecoxib was withdrawn by the manufacturers and most authorities now recommend that COX-2 specific drugs are not used in preference to non-selective ones, unless they are specifically indicated, and only after a full assessment of the cardiovascular risk.⁷ For this reason in countries that have licensed parecoxib and ketorolac, it is only for short-term postoperative pain relief.

Renal

In patients with heart failure, chronic renal failure and/or hypovolaemia, renal blood flow is much more dependent on prostaglandin-induced vasodilatation than it would be in a healthy person. As a result of this, NSAID induced reduction in prostaglandin levels can precipitate acute renal failure. The inhibition of the prostaglandins normally inhibiting anti-diuretic hormone production leads to increased sodium and water retention with the risk of oedema and/or hypertension. Consequently, all NSAIDs are contraindicated in patients with heart failure.

Obstetrics

Prostaglandins are important for initiating labour and NSAID usage can lead to prolonged labour and a NSAID (commonly rectal

indomethacin) is sometimes used as a tocolytic in premature labour. In this context there are potentially serious side effects including foetal oliguria, and premature closure of the ductus arteriosus. Normally patency of the ductus arteriosus is maintained by PGE₂ and NSAID-induced closure in utero can lead to pulmonary hypertension and myocardial infarction. NSAID usage may increase the risk of miscarriage. The effect seems to be greatest if NSAIDs are used for more than a week and around the time of conception.⁸

Hypersensitivity reactions

Hypersensitivity reactions to NSAIDs may manifest as a spectrum from urticaria and rhinitis to bronchospasm, angio-oedema and in extreme cases hypotension and shock. The reactions seen in patients with no history of asthma are thought to be immune mediated, whereas the bronchospasm sometimes seen in asthmatics is not.

The terms aspirin exacerbated respiratory disease (AERD) or aspirin induced asthma (AIA) refer to a worsening of asthma following dosage. A possible mechanism is the build-up of arachidonic acid as a result of COX inhibition, with the result that it is converted to leukotrienes (by lipoxygenase) which acts as a bronchoconstrictor. These individuals are thought to have a discrete disease entity associated with nasal polyps. There is a strong cross reactivity between other NSAIDs, although COX-2 selective NSAIDs appear to be safe.⁹ The estimated prevalence of AERD is 3% when based on population studies but around 20% when based on provocation testing but paediatric prevalence is 2% to 5%.

Drug interactions

NSAIDs can interact with other drugs in various ways. Firstly, as a result of their potential effect on renal function the plasma levels of other drugs may be affected (e.g. lithium). Secondly, NSAIDs may compound the effects of another drug. For example, patients taking an NSAID and warfarin are at greater risk of severe haemorrhage as both drugs exert an anti-coagulant effect. Thirdly, NSAIDs can interact pharmacologically with another drug to alter its effect. An example of this is the elevated international normalised ratio (INR) which may occur in patients taking warfarin and a concomitant NSAID.

Miscellaneous

Reyes syndrome is characterised by encephalopathy and fatty degeneration of the liver, usually occurring after a viral like illness. It is more common in children and associated with aspirin ingestion during the early viral part of the illness. Most countries do not recommend the use of aspirin in children under 16 with fever.

FURTHER READING

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Pharmacology of Opioids

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DEFINITIONS

Opium A mixture of alkaloids from the poppy plant - *Papaver somniferum*.

Opioid Any naturally occurring, semi-synthetic or synthetic compound that binds specifically to opioid receptors (see below) and shares the properties of one or more of the naturally occurring endogenous opioids.

Opiate Any naturally occurring opioid derived from opium (e.g. morphine).

Narcotic From the Greek meaning 'to numb or deaden'. It is often used to denote an opioid but also widely used to describe drugs of addiction and hence includes non-opioid compounds.

MECHANISM OF ACTION

Opioids produce their actions at a cellular level by activating opioid receptors. These receptors are distributed throughout the central nervous system (CNS) with high concentrations in the nuclei of tractus solitarius, peri-aqueductal grey area (PAG), cerebral cortex, thalamus and the substantia gelatinosa (SG) of the spinal cord. They have also been found on peripheral afferent nerve terminals and many other organs. The efficacy of centrally applied opioids is well recognized, but when applied peripherally, for example in post-traumatic and inflammatory states, their actions are less reliable. Opioid receptors are coupled with inhibitory G-proteins and their activation has a number of actions including: closing of voltage sensitive calcium channels; stimulation of potassium efflux leading to hyperpolarization and reduced cyclic adenosine monophosphate production. Overall, the effect is a reduction in neuronal cell excitability that in turn results in reduced transmission of nociceptive impulses.

Pure opioid agonists (morphine, diamorphine, pethidine and fentanyl) bind to opioid receptors avidly and demonstrate high intrinsic activity at the cellular level as described above. Partial opioid agonists (buprenorphine, pentazocine) bind to opioid receptors, but produce a sub-maximal effect compared to pure agonists and so have less intrinsic activity associated with receptor binding. Opioid antagonists (naloxone,

naltrexone), have receptor affinity but no intrinsic activity.

OPIOID RECEPTORS

Since their identification, opioid receptors have had a variety of names. The following is the current nomenclature for identification of the opioid receptors, approved by the International Union of Pharmacology.

MOP - μ (mu) opioid peptide receptor

KOP - κ (kappa) opioid peptide receptor

DOP - δ (delta) opioid peptide receptor

NOP (nociceptin orphanin FQ peptide receptor)

The sigma receptor is no longer classified as an opioid receptor as it does not meet all the criteria to be described as one. A number of different subtypes of each receptor exist; two MOP, three KOP, and two DOP subtypes.

OPIOIDS

Naturally occurring opioid compounds are found in plants (e.g. morphine) and produced in the body (endogenous opioids), where they are widely distributed throughout the central nervous system (CNS). These endogenous compounds are peptides that have variable potency and are preferentially bound by different opioid receptors. They have numerous actions including modulation of pain and control of the cardiovascular system, particularly in shock. Although of interest to pharmacologists, endogenous opioids currently have no clinical role. Synthetic and semi-synthetic opioids are widely used clinically, primarily for their analgesic actions. They exert their effect via the same receptors. Endogenous opioid peptides and commonly used opioid drugs, along with their selectivity (affinity) for different types of opioid receptors, are shown in Table 1.

CLASSIFICATION OF OPIOIDS

Several classifications have been proposed (Table 2).

- **Traditional** - based upon analgesic potency
- **Origin of drug** - i.e. naturally occurring or manufactured

Summary

Opioid drugs are widely used as moderate to strong analgesic agents. The pharmacokinetic properties of different agents determine their analgesic and side effect profiles. Many agents that have fallen from favour in more developed countries are still widely used in poorly-resourced settings and so knowledge of their advantages and disadvantages is essential.

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Table 1. Opioids and their selectivity for different opioid receptors

Opioid	Receptor type			
	MOP	KOP	DOP	NOP
Endogenous				
Beta-endorphin	+++	+++	+++	-
Leu-enkephalin	+	-	+++	-
Dynorphin A& B	++	+++	+	+
OFQ	-	-	-	+++
Clinical drugs				
<i>Agonists</i>				
Morphine	+++	+	+	-
Pethidine	+++	+	+	-
Diamorphine	+++	+	+	-
Fentanyl	+++	+	-	-
<i>Partial agonists</i>				
Buprenorphine	++	+	-	-
Pentazocine	-	++	-	-
<i>Antagonists</i>				
Naloxone	+++	++	++	-
Naltrexone	+++	++	++	-

+ = low affinity, ++ = moderate affinity, +++ = high affinity, - = no affinity.

- **Function** - their action at the opioid receptor.

In the traditional classification, the 'strong' group includes drugs that are pure agonists, whereas intermediate group includes partial agonists.

Table 2. Classification of opioids

Traditional	Origin	Function
Strong morphine pethidine fentanyl alfentanil remifentanil sufentanil	Naturally occurring morphine codeine papavarine thebaine	Pure agonists morphine fentanyl alfentanil remifentanil sufentanil
	Semisynthetic diamorphine dihydrocodeine buprenorphine	Partial agonist buprenorphine
Intermediate buprenorphine pentazocine butorphanol nalbuphine		Agonists-antagonists pentazocine nalbuphine nalorphine
Weak codeine	Synthetic <i>Phenylpyperidines:</i> pethidine, fentanyl, alfentanil, sufentanil <i>Diphenylpropylamines:</i> methadone, dextropropoxyphene <i>Morphinans:</i> butorphanol, levorphanol <i>Benzomorphans:</i> pentazocine	Pure Antagonists naloxone naltrexone

PHARMACOLOGICAL ACTIONS OF OPIOID AGONISTS

Central nervous system

Analgesia

- Most effective in relieving dull, continuous and poorly localised pain arising from deeper structures, for example the gut. Less effective against superficial and sharp pain.
- Neuropathic pain can be very resistant, but patients may report that pain is still present, but the intensity is decreased and it no longer bothers them as much.

Sedation

- Drowsiness, feeling of heaviness and difficulty in concentrating are common.
- Sleep may occur with relief of pain, although they are not true hypnotics.

Euphoria and dysphoria

- Morphine and other opioids cause a sense of contentment and well being (euphoria). If there is no pain, morphine may cause restlessness and agitation (dysphoria).

Hallucinations

- These are more common with KOP agonists, but morphine and other MOP agonists may also cause hallucinations.

Tolerance and dependence

- Tolerance is the decrease in effect seen despite maintaining a given concentration of a drug. The mechanism is not fully understood but could involve down regulation of opioid receptors or decreased production of endogenous opioids.
- Dependence exists when the sudden withdrawal of an opioid, after repeated use over a prolonged period, results in various physical and

psychological signs. These include; restlessness, irritability, increased salivation, lacrimation and sweating, muscle cramps, vomiting and diarrhoea.

Cardiovascular system

Mild bradycardia

- Common as a result of decreased sympathetic drive and a direct effect on the sino-atrial (SA) node.

Peripheral vasodilatation

- Caused by histamine release and reduced sympathetic drive may result in a slight fall in blood pressure that may be significant in hypovolaemic patients.

Respiratory system

Respiratory depression

- Mediated via MOP receptors at the respiratory centres in the brainstem.
- Respiratory rate falls more than the tidal volume and the sensitivity of the brain stem to carbon dioxide is reduced. Its response to hypoxia is less affected but if hypoxic stimulus is removed by supplemental oxygen then respiratory depression may be augmented.
- Concurrent use of other CNS depressants, for example benzodiazepines or halogenated anaesthetic, may cause marked respiratory depression.

Cough suppression

- Codeine suppresses coughing to a degree similar to morphine, but has lesser analgesic activity.
- Morphine and diamorphine are used in paroxysmal nocturnal dyspnoea, as they produce sedation, reduce preload and depress abnormal respiratory drive.

Gastrointestinal System

- Stimulation of the chemoreceptor trigger zone causes nausea and vomiting.

- Smooth muscle tone is increased but motility is decreased resulting in delayed absorption, increased pressure in the biliary system (spasm of sphincter of Oddi) and constipation.

Endocrine System

- The release of ACTH, prolactin and gonadotrophic hormone is inhibited. Secretion of ADH is increased.

Ocular effects

- MOP and KOP receptors in Edinger-Westphal nucleus of oculomotor nerve are stimulated by opioids resulting in constriction of the pupils (meiosis).

Histamine release and itching

- Some opioids cause histamine release from mast cells resulting in urticaria, itching, bronchospasm and hypotension.
- Itching occurs most often after intrathecal opioids and is more pronounced on the face, nose and torso.
- The mechanism is centrally mediated and may be reversed by naloxone.

Muscle rigidity

- Large doses of opioids may occasionally produce generalized muscle rigidity especially of thoracic wall and interfere with ventilation.

Immunity

- The immune system is depressed after long-term opioid abuse.

Effects on pregnancy and neonates

- All opioids cross the placenta and if given during labour, can cause neonatal respiratory depression.
- Chronic use by the mother may cause physical dependence in utero and lead to a withdrawal reaction in the neonate at birth that can be life threatening.
- There are no known teratogenic effects.

PHARMACOKINETICS OF OPIOID AGONISTS

There is substantial variability (3-5 fold) in the clinical response

Table 3. Pharmacokinetics of commonly used opioids

	Morphine	Pethidine	Fentanyl	Alfentanil	Remifentanil
pKa	8.0	8.5	8.4	6.5	7.1
Unionised at pH 7.4 (%)	23	5	9	90	68
Plasma protein bound (%)	30	40	84	90	70
Terminal half life (hrs)	3	4	3.5	1.6	0.06
Clearance (ml.min ⁻¹ .kg ⁻¹)	15-30	8-18	0.8-1.0	4-9	30-40
Volume of distribution (l.kg ⁻¹)	3-5	3-5	3-5	0.4-1.0	0.2-0.3
Relative lipid solubility	1	28	580	90	50

to opioids due to their pharmacokinetics and pharmacodynamics. Pharmacokinetic properties of the opioids commonly used in anaesthesia are displayed in Table 3.

Opioids are weak bases (pKa 6.5-8.7). In solution, they dissociate into ionized and unionized fractions, the relative proportions depend upon the pH of the solvent and their pKa. The unionized fraction is more diffusible than ionized form. In the acidic environment of stomach, opioids are highly ionized and therefore poorly absorbed. Conversely, in the alkaline small intestine, they are predominantly unionized and are readily absorbed. However, many opioids then undergo extensive first-pass metabolism in the intestinal wall and liver, resulting in low oral bioavailability. High lipid solubility facilitates opioid transport into the biophase or site of action. Consequently, high lipid solubility confers a more rapid onset of action.

Drugs with high lipid solubility, high unionized fraction or low protein binding in the plasma, demonstrate large volumes of distribution. Most opioids are extensively distributed in the body and their volumes of distribution exceed total body water. Small intravenous doses of short-acting opioids (like alfentanil, sufentanil or fentanyl) produce a short duration of action because plasma (and brain) concentrations remain above the threshold for therapeutic action for only a brief period as the drug rapidly redistributes from the CNS to other tissues. Larger doses produce longer durations of action because plasma concentrations remain above the threshold at the completion of drug redistribution and depend upon the slower elimination process to be reduced below the threshold level.

Opioids are metabolized mainly in the liver to both active and inactive compounds that are excreted in urine and bile. Morphine and other opioids are excreted partly in the bile as water-soluble glucuronides. In the gut, these glucuronides are metabolized by the normal gut flora to the parent opioid compound and reabsorbed (entero-hepatic recirculation). Highly lipid soluble opioids, for example fentanyl, may diffuse from the circulation into the stomach mucosa and lumen, where they are ionized and concentrated because of the low pH. Later, gastric emptying and reabsorption from the small intestine may produce secondary peak effect (gastro-enteric recirculation). Extra-hepatic metabolism is important for some opioids; the kidneys play a vital role in conjugating morphine, whereas blood and tissue esterases are responsible for remifentanyl metabolism.

Opioids differ substantially in their durations of action. Explanations for these differences are complex and not always evident from their clearance and terminal half-lives. For example, an analgesic dose of morphine lasts longer than a dose of fentanyl producing an equivalent degree of analgesia; yet the half-life for morphine is shorter than fentanyl. In the case of morphine, its relatively long duration of action is a reflection of its relatively low lipid solubility and slow diffusion out of CNS tissue. Once it enters blood it is effectively cleared from plasma.

INDIVIDUAL OPIOIDS

Morphine

Morphine is a naturally occurring phenanthrene derivative. It is the standard drug against which all other opioids are compared.

Dose

- Morphine can be given orally, intramuscularly (IM), intravenously (IV), subcutaneously (SC), rectally, epidurally and intrathecally.
- The intramuscular dose is 0.1-0.2mg.kg⁻¹, time to peak effect is 30-60 minutes and duration of action is 3-4 hours. Intravenous administration should be titrated to effect (usually 1-2mg boluses), but the total dose is similar. The onset of action is slightly more rapid with following IV administration, as the main factor responsible for its latency is low lipid solubility and slow penetration of blood brain barrier. Morphine may be given epidurally at 10% and intrathecally at 1% of the parenteral dose.

Pharmacokinetics

- Morphine is extensively metabolized by the gut wall and the liver to morphine-3-glucuronide (M3G) (70%), morphine-6 glucuronide (M6G) (10%) and to sulphate conjugates. M6G is 10-20 times more potent than morphine and is normally excreted in urine.
- It accumulates in renal failure and accounts for increased sensitivity to morphine.
- Neonates are more sensitive than adults to morphine due to reduced hepatic conjugating capacity.
- In the elderly, owing to reduced volume of distribution, peak plasma level of morphine is higher compared to younger patient.

Effects

- The main effects are mediated through MOP receptors. It is a potent analgesic with good sedative and anxiolytic properties. It may cause euphoria, dysphoria and hallucination. It produces respiratory depression and cough suppression.
- It has minimal effect on cardiovascular system and may produce bradycardia and hypotension. Nausea and vomiting are common side-effects. Histamine release may lead to rash, itching and bronchospasm (in susceptible patients). Meiosis is common. Tolerance and dependence may develop.

Papaveretum

Papaveretum is a preparation containing a mixture of hydrochloride salts of opium alkaloids: morphine hydrochloride, codeine hydrochloride and papaverine hydrochloride. Prior to 1993, the preparation also contained noscapine, however this was removed after it had been shown to be teratogenic in animal studies.

Dose

- It can be given subcutaneously, intramuscularly or intravenously. 15.4mg of papaveretum contains 10mg of morphine.
- It is used for moderate to severe pain and preoperative sedation.

Effects

- In comparison with morphine, it provides greater degree of sedation for a given level of analgesia with fewer gastrointestinal side-effects.

- Higher doses of papaveretum are associated with transient but severe headache. This effect, linked most likely to its papaverine content, reduces the compound's addiction potential.
- Most anaesthetists feel that the added expense of the mixture is not justified because in the concentration used, morphine is the only active ingredient.

Codeine

Codeine is a natural opioid and one of the principal alkaloids of opium. It has very low affinity for opioid receptors.

Dose

- Can be given orally and IM. The dose for an adult is 30-60mg by either route and can be repeated at 6 hour intervals, if required. Varying doses of codeine (8-30mg) are commonly incorporated with NSAIDs in compounds employed in the treatment of mild to moderate pain.
- Codeine is also used in antitussive and antidiarrhoeal preparations.

Pharmacokinetics

- Oral bioavailability of codeine is 50%. About 10% is metabolized to morphine and the rest is metabolized to inactive conjugated compounds.
- Metabolism to morphine depends on an isoform of cytochrome p450, which exhibits polymorphism, thus poor metabolizers (approximately 10% people) may experience minimal pain relief.

Effects

- It causes little euphoria and has low abuse potential. Codeine is less sedative and less likely to cause respiratory depression than morphine. It may cause disorientation and excitement.
- Constipation is common side effect.
- Dihydrocodeine is a semi-synthetic derivative of codeine with similar pharmacologic effects.
- Oxycodone is more effective, but has higher abuse potential.

Diamorphine (heroin)

A semi-synthetic opioid, the diacetylated analogue of morphine. It is 1.5-2.0 times more potent than morphine. It is a pro-drug and is converted to the active components of acetylmorphine and morphine by esterases in the liver, plasma and central nervous system.

Dose

- Diamorphine can also be given by the same routes as morphine in approximately half the dose. Due to its higher lipid solubility, it is less likely than morphine to cause delayed respiratory depression when used epidurally or intrathecally.
- It can be administered as hydrochloride salt by IM or SC infusion in a smaller volume of solution than an equivalent dose of morphine. This is an important consideration for patients with terminal malignant disease who may require large doses of opioid for pain relief.

Pharmacokinetics

- Diamorphine is 200 times more lipid soluble than morphine and, therefore, passes more rapidly across the blood-brain barrier into the CNS where it is converted to morphine. Therefore, it has more analgesic potency and a more rapid onset of action than morphine.
- Because of the extensive first pass metabolism, it has low bio-availability.

Effects

- It shares common opioid effects with morphine. It is associated with an increased tendency to cause euphoria and dependency.
- May cause less nausea and vomiting than morphine.

Pethidine (mepiridine)

It is a synthetic phenylpyperidine derivative and was originally developed as an antimuscarinic agent.

Dose

- Pethidine is available as 50mg tablets and ampoules of different strength (10mg.ml⁻¹ and 50mg.ml⁻¹).
- For acute pain, it can be administered orally (50-150mg), SC (50-100mg), IM (50-100mg) or IV (25-100mg). The doses can be repeated every 4 hours.

Pharmacokinetics

- Pethidine is 30 times more lipid soluble than morphine. Oral bioavailability is 50%.
- It is metabolized in the liver by ester hydrolysis to norpethidine and pethidinic acid that are excreted in the urine and therefore accumulate in renal failure. At higher concentration, norpethidine can produce hallucination and convulsions.
- Pethidinic acid is an inactive compound.
- Pethidine is often used for labour analgesia. It readily crosses the placenta, and a significant amount reaches to the foetus over several hours.

Effects

- There are some pharmacological differences from morphine. It produces tachycardia, dry mouth and less marked meiosis. However as is the case with morphine, a significant decrease in BP may occur when pethidine is administered to elderly or hypovolaemic patients.
- It may produce less biliary tract spasm than morphine. Pethidine is absolutely contraindicated in patients on monoamine oxidase inhibitors (MAOI), as serious side effects like hypotension or hypertension, hyperpyrexia, convulsion and coma may occur.
- The underlying mechanism is not clear but may involve reduced metabolism of pethidine by MAOI and pethidine's effect on turnover of 5- hydroxytryptamine in the brain.

Fentanyl

It is a synthetic phenylpyperidine derivative and is 100 times more potent than morphine.

Dose

- Fentanyl is available as a colourless solution for injection in 2 and 10ml ampoules containing 50mcg per ml.
- When given in small doses ($1-2\text{mcg.kg}^{-1}$), it has rapid onset and a short duration of action (30 minutes). Such doses are used intravenously for pain associated with minor surgery. In small doses it has little sedative effect.
- Higher doses are used to obtund sympathetic response to laryngoscopy and intubation.
- Fentanyl has been used to augment effects of local anaesthetics in spinal and epidural analgesia at 10-25mcg and 25-100mcg doses respectively.
- Fentanyl is also available as a transdermal patch for chronic pain conditions and as a lollipop to premedicate children.

Pharmacokinetics

- Fentanyl is 500 times more lipid soluble than morphine, consequently it is rapidly and extensively distributed in the body (volume of distribution 4l.kg^{-1}). At small doses ($1-2\text{mcg.kg}^{-1}$), plasma and CNS concentrations may decrease quickly to below an effective level during the rapid distribution phase.
- However, following prolonged administration or with high doses, its duration of action is significantly prolonged. In these circumstances, the distribution phase is complete while the plasma concentration is still high. Recovery from the effect of the drug then depends on its slow elimination from the body (terminal half life 3.5 hours).
- Fentanyl is predominantly metabolized in the liver to norfentanyl which is inactive. The metabolite is excreted in the urine over a few days.

Effects

- Many properties of fentanyl are similar to morphine. It produces respiratory depression in a dose-dependent manner.
- Large doses (50- 100 microgram/kg) have been used for cardiac surgery to obtund metabolic stress response. At such high doses, sedation is profound and unconsciousness may occur. In addition, muscular rigidity of the chest wall may affect ventilation.

Alfentanil

Alfentanil is a synthetic phenylpiperidine derivative structurally related to fentanyl; it has 10-20% of its potency.

Dose

- Alfentanil is available as colourless solution in the concentrations of 500mcg.ml^{-1} or 5mg.ml^{-1} . It may be administered intravenously as either a bolus or continuous infusion.
- Bolus doses (10mcg.kg^{-1}) are useful for short term analgesia and attenuation of the cardiovascular response to intubation. Continuous infusions ($0.5-2.0\text{mcg.kg}^{-1}.\text{min}^{-1}$) are used in the intensive care unit for sedation in patients on mechanical ventilation.

Pharmacokinetics

- Although it has much lower lipid solubility than fentanyl, the

lower pKa of alfentanil (6.5 versus 8.4 for fentanyl) means that more alfentanil is present in the unionized form compared to fentanyl (89% compared to 9%). Consequently, its onset of action is more rapid.

- Because of its lower lipid solubility, less alfentanil is distributed to muscles and fat. Hence, its volume of distribution is relatively small and more of the dose remains in blood from which it can be cleared by the liver.
- Even though alfentanil has a lower clearance rate, this is more than offset by its reduced volume of distribution and its half life is relatively short.

Effects

- Most effects of alfentanil are similar to fentanyl but with quicker onset and shorter duration of action.

Remifentanyl

It is a synthetic phenylpiperidine derivative of fentanyl with similar potency but is ultra short-acting.

Dose

- It is available as white crystalline powder in glass vial containing 1, 2 or 5mg remifentanyl hydrochloride.
- A range of infusion rates ($0.05-3.0\text{mcg.kg}^{-1}.\text{min}^{-1}$) are used during maintenance of anaesthesia with controlled ventilation.

Pharmacokinetics

- Remifentanyl is rapidly broken down by non-specific plasma and tissue esterases resulting in a short elimination half life (3-10 minutes).
- It is context insensitive, in that the half life, clearance and distribution are independent of duration and strength of infusion.

Effects

- Certain properties of remifentanyl like rapid onset, rapid offset, organ independent metabolism and lack of accumulation make it suitable for use during various surgical procedures. However, it should be used cautiously at higher rates of infusion as serious side effects for example bradycardia, hypotension, apnoea and muscle rigidity may occur.
- Since there is no residual effect, alternative postoperative analgesic regimen should be established before infusion is terminated.

Tramadol

Tramadol is phenylpiperidine analogue of codeine. It is weak agonist at all opioid receptors with 20-fold preference for MOP receptors. It inhibits neuronal reuptake of norepinephrine. It potentiates release of serotonin and causes descending inhibition of nociception.

Dose

- Oral and parenteral dosage requirements are similar, 50-100mg 4 hourly.

Pharmacokinetics

- Tramadol has high oral bioavailability of 70% which can increase

to 100% with repeated doses due to reduction in first pass effect. It is 20% bound to plasma proteins.

- It is metabolized in the liver by demethylation into a number of metabolites - only one of them (O-desmethyltramadol) has analgesic activity. Its volume of distribution is 4 l.kg^{-1} and its elimination half-life is 4-6 hours.

Effects

- In equi-analgesic dose to morphine, tramadol produces less respiratory and cardiovascular depression than morphine.
- Constipation is less common, however tramadol shares most of the common side effects of other opioids (e.g. vomiting, drowsiness and ambulatory dizziness).
- Tramadol is contra-indicated in patients on MAOI or with a history of epilepsy.

Methadone

A potent opioid analgesic that is well absorbed with good oral bioavailability (75%). However, its main use is as a substitute for opioids, for example diamorphine (heroin) in addicts because its slow onset and offset reduces the incidence of withdrawal symptoms. It is itself addictive.

PARTIAL OPIOID AGONISTS

These drugs have affinity for opioid receptors but low intrinsic activity compared to full agonists. Because of their reduced activity, they are able to antagonise or reduce the responsiveness of a pure agonist like morphine when acting at the same receptor. In other words, a higher dose of a pure agonist is required in presence of partial agonist, in order to obtain full agonist response. They can be further divided into two groups:

1. **Mixed agonist-antagonist.** They exert agonist effects at one opioid receptor and antagonistic effects at the other. Examples are pentazocine, nalbuphine and meptazinol.
2. Drugs that do not display antagonistic effects but have diminished effects at opioid receptors.

Meptazinol

Meptazinol is a synthetic analgesic with mixed agonist-antagonist activity at opioid receptors. It also has an action via central cholinergic pathways that may contribute to analgesia. It produces less respiratory depression because of its selectivity for MOP-1 receptors. Its main disadvantage is a high incidence of nausea and vomiting, that can be reduced by administration of antimuscarinic drugs. It is one-tenth as potent as morphine. It has rapid onset of action that lasts for 2-4 hours.

Buprenorphine

Buprenorphine is 30 times more potent than morphine. It is highly lipid soluble, and is well absorbed sublingually. It has low oral bioavailability. Although its terminal half-life is 3-4 hours, it has a much longer duration of action (up to 8 hours). In general,

buprenorphine and morphine produce similar effects and side effects. As buprenorphine has extremely high affinity for MOP receptors, its effects are not completely reversed by naloxone (see opioid antagonists). Respiratory depression may need to be treated with doxapram. Nausea and vomiting are severe and prolonged.

Pentazocine

Pentazocine has 25% of the analgesic potency of morphine. It is not very effective in relieving severe pain, and this may be partly because of absence of euphoriant effect. It produces an increase in heart rate and blood pressure. Nausea, vomiting, bizarre dreams and hallucinations are more common than morphine.

OPIOID ANTAGONISTS

Naloxone and its longer acting derivative naltrexone occupy opioid receptors, but they have essentially no intrinsic activity at these receptors. Moderate doses administered in the absence of an opioid produce no effect; large doses, however, may have effects in which antagonism of endorphins may play a role.

Naloxone

Naloxone is a pure opioid agonist and will reverse opioid effects at MOP, KOP and DOP receptors, although its affinity is highest at MOP receptors.

It is the drug of choice for the treatment of opioid induced respiratory depression. The usual dose is 200-400mcg intravenously, titrated to effect. It is imperative the naloxone be administered slowly to avoid reactive pulmonary hypertension with the development of acute pulmonary oedema probably from antagonism of endogenous opioid effects. Smaller doses ($0.5\text{--}1.0\text{ mcg.kg}^{-1}$) may be titrated to reverse undesirable effects of opioids, for example itching associated with the intrathecal or epidural administration of opioids, without significantly affecting the level of analgesia. The duration of effective antagonism is limited to around 30 minutes and therefore longer acting agonists will outlast this effect and further bolus doses or an infusion ($5\text{--}10\text{ mcg.kg}^{-1}.\text{h}^{-1}$) will be required to maintain reversal. Caution must be used in opioid addicts as giving naloxone may cause an acute withdrawal state with hypertension, pulmonary oedema and cardiac arrhythmias. Antanalgesic effects may be observed in opioid naïve subjects who are given naloxone.

Naltrexone

Naltrexone has similar mechanism of action, but has few pharmacokinetic advantages compared to naloxone. It has a longer half-life and is effective orally for up to 24 hours. It has been used to treat opioid addiction and compulsive eating with morbid obesity.

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Originally published in Anaesthesia Tutorial of the Week (2005)

Local Anaesthetic Pharmacology

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Summary

Local anaesthetic drugs are used widely for the provision of anaesthesia and analgesia both intra- and post-operatively.

Understanding the pharmacology of these agents as a group, as well as the differences between specific drugs, enables the anaesthetist to use them safely to maximum effect. This article focuses on the basic structure and function of local anaesthetics. Learning will be improved by trying to answer the questions posed in the text before moving on. More detail can be found in the "Further reading" section at the end.

DEFINITION OF A LOCAL ANAESTHETIC

A local anaesthetic can be defined as a drug which reversibly prevents transmission of the nerve impulse in the region to which it is applied, without affecting consciousness. There are many drugs which exert local anaesthetic activity in addition to their main clinical uses, but this article will focus on those drugs which are principally used for their local anaesthetic properties.

STRUCTURAL CLASSIFICATION OF LOCAL ANAESTHETICS

Local anaesthetics generally have a lipid-soluble, hydrophobic aromatic group and a charged, hydrophilic amide group. The bond between these two groups determines the class of the drug, and may be amide or ester. Examples of amides include lignocaine, bupivacaine and prilocaine. Examples of esters include cocaine and amethocaine.

CLINICALLY SIGNIFICANT DIFFERENCES BETWEEN ESTERS AND AMIDES

The ester linkage is more easily broken than the amide bond so the ester drugs are less stable in solution and cannot be stored for as long as amides. Amide anaesthetics are also heat-stable and can therefore be autoclaved; esters cannot. The metabolism of most esters results in the production of para-aminobenzoate (PABA) which is associated with allergic reactions. Amides, in contrast, very rarely cause allergic phenomena. For these reasons amides are now more commonly used than esters.

LOCAL ANAESTHETICS AS ISOMERS

Local anaesthetics may also be considered in terms of their stereoisomerism. This term describes the existence of molecules with the same molecular and structural formula, but different spatial orientation around a particular atom, the chiral centre. This is analogous the right and left foot being mirror images of each other. Stereoisomerism occurs in the case of bupivacaine which has two stereoisomers, known as R and S forms, and also in the case of prilocaine. The combination of equal amounts of the two stereoisomers of a particular drug is known as a racemic mixture.

Why might isomerism be important?

The different arrangements of the R and S forms

of bupivacaine are thought to be associated with differences in potency and side-effect profile. This is easy to understand if you were to try and put your right foot in your left shoe – it doesn't work as well and causes side effects (pain)! This is the reason why more drugs are being prepared as a single stereoisomer such as levobupivacaine. Another familiar example of this is ketamine.

In contrast amethocaine (an ester) and lignocaine are achiral, i.e. they have no stereoisomers.

THE MECHANISM OF ACTION OF LOCAL ANAESTHETICS

Local anaesthetics disrupt ion channel function within the neurone cell membrane preventing the transmission of the neuronal action potential. This is thought to occur via specific binding of the local anaesthetic molecules (in their ionised form) to sodium channels, holding them in an inactive state so that no further depolarisation can occur. This effect is mediated from within the cell; therefore the local anaesthetic must cross the cell membrane before it can exert its effect.

A second mechanism is also thought to operate, involving the disruption of ion channel function by the incorporation of local anaesthetic molecules into the cell membrane (the membrane expansion theory). This is thought to be mediated mainly by the unionised form acting from outside the neuron. Nerve fibres differ in their sensitivity to local anaesthetics. Small nerve fibres are more sensitive than large nerve fibres while myelinated fibres are blocked before non-myelinated fibres of the same diameter. Thus the loss of nerve function proceeds as loss of pain, temperature, touch, proprioception, and then skeletal muscle tone. This is why people may still feel touch but not pain when using local anaesthesia.

THE IMPORTANCE OF THE pKa OF A LOCAL ANAESTHETIC DRUG

All local anaesthetic agents are weak bases, meaning that they exist in two forms: unionised (B) and ionised (BH⁺). The pKa of a weak base defines the pH at which both forms exist in equal amounts. As the pH of the tissues differs from the pKa of the specific drug, more of the drug exists either in its charged or uncharged

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form. This is expressed in the Henderson-Hasselbach equation:

$$\text{pKa} - \text{pH} = \log \frac{[\text{BH}^+]}{[\text{B}]}$$

where [B] is the concentration of unionised and [BH⁺] the concentration of ionised drug.

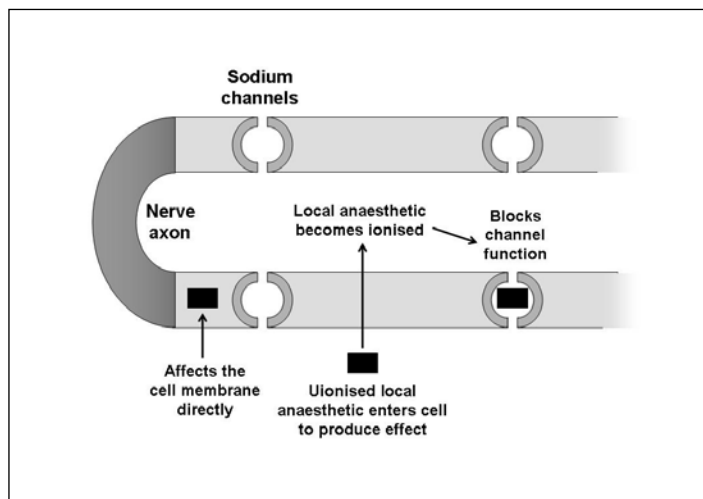


Figure 1. The mechanism of action of local anaesthetic agents

How may the pKa of a local anaesthetic influence its speed of onset?

The pKa of a local anaesthetic determines the amount which exists in an ionised form at any given pH. At physiological pH (7.4) all local anaesthetics are more ionised than unionised (as all the pKa values are greater than 7.4). However the proportions vary between the drugs: lignocaine has a pKa of 7.9 and is approximately 25% unionised at pH 7.4. Bupivacaine has a pKa of 8.1 and hence less of the drug is unionised at pH 7.4 (about 15%).

As the drug must enter the cell in order to have its effect it must pass through the lipid cell membrane. Unionised drug will do this more readily than ionised drug. Therefore the drug which is more unionised at physiological pH will reach its target site more quickly than the drug which is less so. This explains why lignocaine has a faster onset of action than bupivacaine.

Can this theory explain why local anaesthetics often don't work in infected tissue?

The relevant feature of infected tissue is that it tends to be a more acidic environment than usual. As the pH is reduced the fraction of unionised local anaesthetic is reduced and consequently the effect is delayed and reduced. Infected tissue may also have an increased blood supply and hence more anaesthetic may be removed from the area before it can affect the neurone.

How else may the physicochemical characteristics of a local anaesthetic affect its function?

Physicochemical features such as the aromatic ring structure and hydrocarbon chain length of a particular local anaesthetic determine the lipid solubility of the drug and hence its potency. This makes sense since the more lipid soluble drug penetrates the cell membrane more

easily to exert its effect. The more potent the drug, the smaller the amount required to produce a given effect. Thus bupivacaine – which is highly lipid soluble – is approximately four times more potent than lignocaine. This is reflected in the different preparations available of these two drugs; bupivacaine being more potent is prepared as a 0.1–0.5% solution. Lignocaine conversely is commonly presented as a 1% or 2% solution.

The duration of action of the drug is also related to its structure, primarily to the length of the intermediate chain joining the aromatic and amine groups. However it should be noted that protein binding is probably at least as important a determinant of duration of action. Clearly the molecular structure of the drug also affects protein binding ability and therefore all local anaesthetics differ in the extent to which they are protein-bound. So, for example, lignocaine is approximately 65% protein bound whereas bupivacaine is 95% protein bound. Therefore one can predict that bupivacaine will have a longer duration of action than lignocaine – which is in fact the case. Procaine (an ester), in contrast, is only 6% protein bound and has a very short duration of action.

Differences in protein binding also result in differing duration of unwanted side effects. This is one of the reasons that bupivacaine is considered more toxic than lignocaine.

PHARMACOKINETICS OF LOCAL ANAESTHETICS

Absorption and distribution

Local anaesthetic drugs are administered to the areas around the nerves to be blocked – which include skin, subcutaneous tissues, intrathecal and epidural spaces. Some of the drug will be absorbed into the systemic circulation: how much will depend on the vascularity of the area to which the drug has been applied and intrinsic effects of the drug or its additives on vessel diameter. Some local anaesthetics have vasodilatory effects at low concentrations, increasing their systemic absorption. This is countered in some preparations which include a vasoconstrictor such as adrenaline or felypressin. Cocaine, in contrast, has a vasoconstrictive effect.

The distribution of the drug is influenced by the degree of tissue and plasma protein binding of the drug. As discussed above, the more protein bound the agent, the longer the duration of action as free drug is more slowly made available for metabolism.

Metabolism and excretion

Ester and amide anaesthetics differ in their metabolism. Esters (except cocaine) are broken down rapidly by plasma esterases to inactive compounds and consequently have a short half life. Cocaine is hydrolysed in the liver. Ester metabolite excretion is renal.

Amides are metabolised hepatically by amidases. This is a slower process, hence their half-life is longer and they can accumulate if given in repeated doses or by infusion. Prilocaine is also metabolised extrahepatically.

Which local anaesthetic drugs are more likely to affect the foetus when given in pregnancy and why? How does the situation change if the foetus is compromised?

The esters are metabolised sufficiently rapidly to have minimal effects

on the foetus so little remains in the maternal circulation to cross the placenta. Amide local anaesthetics are more likely to cross the placenta. Of these, placental transfer is greater in those which are less protein-bound (such as lignocaine).

If the foetus is compromised it may become acidotic. In this situation more of the foetal local anaesthetic will be ionised and hence unable to return to the maternal circulation. This phenomenon is known as ion trapping and can result in foetal toxicity. These effects are not likely to be important when small amounts of drug are used during spinal anaesthesia, but may become so when larger amounts are used for epidural anaesthesia or other nerve blocks around the time of delivery.

CLINICAL USES OF LOCAL ANAESTHETICS

Preparations

Local anaesthetics are available as solutions for injection, sprays, creams and gels. They are prepared as the hydrochloride salt to enable them to be dissolved in water (resulting in an acidic solution). Of note, due to new legislation, some of the newer local anaesthetics are described in terms of the quantity of free base present alone, in contrast to the older drugs which are described in terms of the quantity of total hydrochloride salt present. This is why, for example, 10ml of 0.5% bupivacaine (a racemic mixture) contains fewer local anaesthetic molecules than 10ml of 0.5% levobupivacaine. Most local anaesthetic preparations contain a preservative agent such as 0.1% sodium metabisulphite, with or without a fungicide. Multidose vials contain 1mg/ml of the preservative methyl parahydroxybenzoate. The drug may also be combined (by the manufacturer or in some cases the clinician) with other local anaesthetics (e.g. EMLA cream - eutectic mixture of local anaesthetics) or additives designed to enhance their effects. These include adrenaline 1 in 200,000, bicarbonate (eg 0.15ml of 8.4% solution added to 10ml 0.5% bupivacaine) or glucose (usually 80mg.ml⁻¹).

How might addition of epinephrine, bicarbonate and glucose affect the action of local anaesthetics?

Epinephrine acts as a vasoconstrictor. The result is to minimise the vasodilator effect of (for example) lignocaine and decrease the rate at which drug is removed from the site of action by absorption into the systemic circulation. It also reduces traumatic (surgical) blood loss from the site by the same mechanism.

Bicarbonate added to a local anaesthetic increases the pH of the environment when administered. Consequently more drug is present in its unionised form and speed of onset of anaesthesia is increased. Too much bicarbonate however may result in precipitation of the local anaesthetic as the unionised form is much less soluble in water than the hydrochloride salt.

Glucose is added to bupivacaine in order to increase the baricity of the solution to greater than that of CSF. When administered as a spinal anaesthetic this results in more controlled spread of solution within the intrathecal space.

What harmful effects of local anaesthetics do you know?

Potential problems

Local anaesthetics may be toxic if sufficient amounts are absorbed into the systemic circulation. Of these bupivacaine appears to be the most dangerous although all can be harmful. Clinical toxicity appears to relate to the effects of the drug on other excitable membranes in the CNS and cardiovascular systems. CNS effects may include tingling of the lips, slurred speech, reduced level of consciousness and seizures. Cardiac effects on a variety of ion channels may cause arrhythmias and reduced myocardial contractility. In the case of bupivacaine the cardiac effects are particularly difficult to treat since its strong protein binding makes it difficult to displace from the myocardium. In contrast lignocaine may be used clinically for its cardiac effects as an antiarrhythmic.

Unexpected local anaesthetic toxicity can occur where the pharmacokinetics of the drug are altered by comorbidity such as cardiac or hepatic failure (reducing metabolism of the drug), alterations in plasma protein binding, or interactions with other drugs.

Other clinical problems are more specific to particular drugs. The incidence of allergy to PABA, a metabolite of many esters has been mentioned. Prilocaine is metabolised to O-toluidine which can cause methaemoglobinaemia in susceptible individuals. Cocaine is a potent vasoconstrictor and may cause problems in patients already on vasoconstricting drugs such as monoamine oxidase inhibitors.

CONCLUSION

Understanding the pharmacology of local anaesthetics enables the anaesthetist to predict the potency, speed of onset, duration of action and safety of a specific drug in a given clinical situation. This maximises the opportunity for safe and effective use of local anaesthesia in a wide variety of contexts.

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PHYSICS AND EQUIPMENT

130 Gases and Vapours

Ben Gupta

135 Vaporisers

Scott Simpson

141 The Physics of Flow

Paul Clements and Carl Gwinnutt

145 Anaesthetic Breathing Systems

Quentin Milner

150 SI Units

Zoe Brown

151 Humidification

Sampath Shenoy

154 Anaesthetic Gas Scavenging

Matthew Mackenzie

156 Practical Applications of Pulse Oximetry

E Hill, MD Stoneham and S-J Fearnley

160 Pressure and Blood Pressure Monitoring

Claire Todd and Peter Hambley

164 Biological Signals and their Measurement

Zoe Brown and Ben Gupta

170 Respiratory Gas Analysis

Grant McFayden

174 Electricity and Magnetism

David Sanders and Bruce McCormick

182 Heat Production and Loss

Sri Rao and Miraja Rajan

188 Decontamination Procedures for Medical Equipment

Roger Skilton

190 Fires and Explosions in the Operating Room

GA Busato

Gases and Vapours

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BASIC CONCEPTS

All matter exists in one of three states or phases - solid, liquid or gas. When a gas co-exists in equilibrium with its corresponding liquid, the gas is termed a *vapour*. In this situation, molecules are moving from the liquid to the gas phase at the same rate as they are moving from the gas back to the liquid phase. Many liquids, including water, have vapour associated with them at room temperature. As the ambient temperature increases, the number of molecules that exist as a vapour rather than a liquid increases until a new equilibrium is reached. Eventually, at a certain temperature (the boiling point), the entirety of the liquid moves into the gas phase - at this point it is no longer termed a vapour. At temperatures above the boiling point it is still possible to partially convert a gas back to a liquid by increasing the pressure of the gas. But this becomes increasingly difficult, and eventually impossible, to achieve as the temperature of the gas increases. The *critical temperature* is defined as the temperature above which a substance cannot exist in a liquid state.

A related but slightly different concept is the critical pressure. The *critical pressure* is the pressure exerted by a gas at the critical temperature. It can also be thought of as the pressure required to liquefy a gas at the critical temperature. These values are equivalent.

Vapour pressure is the pressure exerted by a vapour when it is in equilibrium with its associated liquid. In anaesthesia the term *saturated vapour pressure* (SVP) is also frequently used, although the term 'saturation' incorrectly implies that vapour is 'dissolved' in the atmosphere. A vapour is a gas and, under normal circumstances, gases are infinitely soluble with respect to one another, i.e. there is no solute or solvent, gases simply mix with one another as if the other gas was not present. This may seem a minor point, but understanding that a vapour is a gas and therefore behaves like one is central to understanding what happens to vapours under different circumstances.

Vapour pressures increase non-linearly with increasing temperature and the *boiling point* of a liquid is defined as the temperature at which the vapour pressure is equal to atmospheric pressure (see Figure 1). Vapour pressures are not affected by atmospheric pressure,

for example the vapour pressure of water at any given temperature is the same at sea level as it would be at the top of Mount Everest. However, boiling points do decrease with increasing altitude and this is simply because the atmospheric pressure decreases, which means that the vapour pressure becomes equal to it at a lower temperature. The *standard boiling point* is the temperature at which the vapour pressure of a liquid equals 1bar (100kPa).

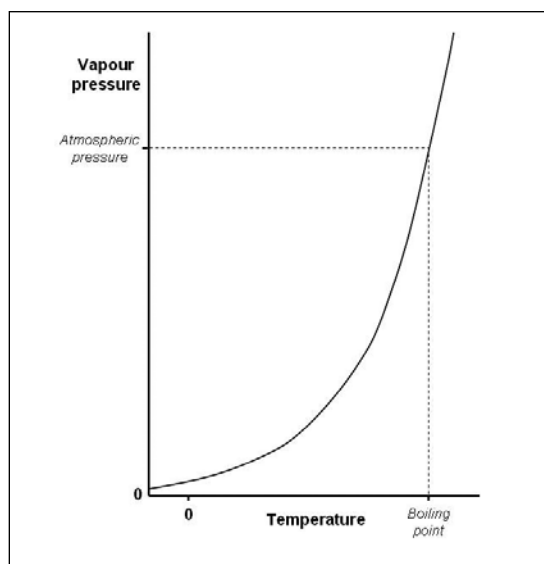


Figure 1. Graph of temperature versus vapour pressure for a typical anaesthetic agent

Similarly, vapour pressures are also strictly independent of the ambient air temperature. In practice however, the ambient air temperature will affect the temperature of the liquid and thus the vapour pressure. This makes sense if you remember that a vapour is just a gas in equilibrium with its associated liquid and therefore follows Dalton's Law (see below) - it behaves independently from the other gases with which it is mixing.

The fact that boiling point decreases with decreasing ambient pressure can be used to test the efficiency of clinical suction devices. The amount by which a suction device can lower the boiling point of a liquid in a sealed container will be related to the drop in pressure the device produces. Substances which have

Summary

The use of inhaled anaesthetic agents was pioneered during the 19th Century and had a huge impact on the development of medicine and surgery. Although a range of different inhaled anaesthetic agents are available in different settings around the world, the principles involved remain unchanged and a good understanding of the properties of commonly used gases and vapours is essential for the safe conduct of anaesthesia.

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low boiling points have high saturated vapour pressures and are often termed 'volatile liquids'.

The final basic concept is the *triple point*. The triple point of a substance is the temperature and pressure at which it exists simultaneously, in thermodynamic equilibrium, as a solid, liquid and gas. For water this occurs at 273.16 K (0.01°C) and 611.7Pa. This is notable only because the triple point of water is the set-point used to define the Kelvin temperature scale, the SI unit of temperature.

THE GAS LAWS

Pressure, volume and temperature

When describing the behaviour of gases the properties of temperature, pressure and volume are related in a consistent manner, which makes it possible to formulate three 'gas laws'. They can be concisely expressed as follows in Figure 2.

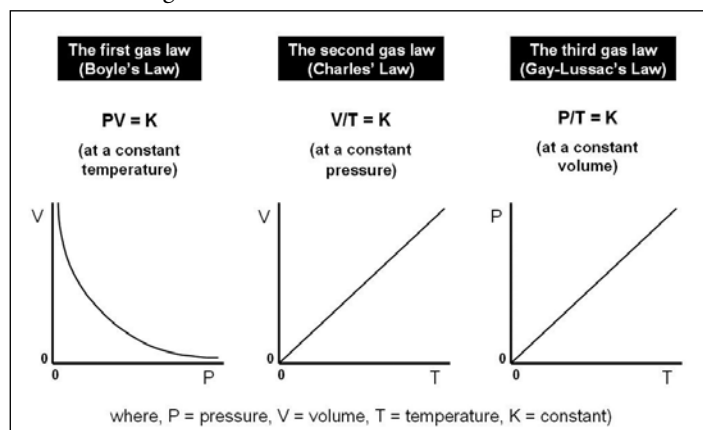


Figure 2. The Gas Laws

Note that a common pitfall is to state that pressure is proportional to volume - in fact it is *inversely* proportional and when plotted produces a hyperbola as can be seen in Figure 2. In the second and third gas laws the variables are proportional to one another and produce a straight line when plotted.

The combined gas law is derived from all three gas laws and is as follows:

$$\frac{PV}{T}$$

or alternatively expressed:

$$\frac{P_1 V_1}{T_1} = \frac{P_2 V_2}{T_2}$$

Providing two of the variables are known, and the third can be assumed to remain constant, the gas laws can be used to calculate changes in one of the known variables when the other alters. For example, if the initial pressure and volume of an oxygen cylinder is 137bar and 1.2litres respectively (and temperature is assumed to remain constant), then the volume of the oxygen at a pressure of 1bar can be calculated. Assuming room pressure is also roughly 1bar then this approximates to the volume of oxygen available to the patient, before the cylinder empties. Furthermore, if the rate of oxygen use is known, then the time remaining for use of that oxygen cylinder can be calculated.

When making these calculations it does not matter which units are used for pressure or volume providing consistency is maintained (see Table 1). Temperature, however, requires a scale that starts at absolute zero, therefore Kelvin must be used.

Unit	Equivalent value
Atmospheres (atm)	1
Bar (bar)	1
Kilopascals (kPa)	101.3
Millimetres of mercury (mmHg)	760
Torr (mmHg 0°C)	760
Centimetres of water (cmH ₂ O)	1033.2
Pounds per square inch (PSI)	14.7

Table 1. Units of pressure. The SI unit of pressure is the pascal (Pa) which is a force of 1Newton per metre squared (N.m⁻²). In practice, however, many different units of pressure are used in anaesthesia. The table above shows equivalent values for all the units of pressure that you are likely to encounter. Gas cylinder pressures are commonly expressed in bar

Avagadro's law

Avagadro's law states that at a constant temperature and pressure a given volume of any gas will contain the same number of molecules. The converse of this is that at a given temperature and pressure, 1 mole of any gas will occupy the same volume (22.4litres at 1 atmosphere and 0°C). Both Avagadro's law and the combined gas law are used to derive the ideal gas law:

$$PV = nRT$$

where, n = number of moles of gas, R = universal gas constant (8.314)

The ideal gas law is of relevance when considering the behavior of nitrous oxide in cylinders (see below).

Henry's Law

Henry's law states that at a constant temperature, the amount of a given gas dissolved in a given liquid is directly proportional to the partial pressure of the gas in contact with the liquid. For any given combination of different gases, liquids and temperatures there is a unique solubility coefficient or constant. Temperature affects the solubility of gases such that at higher temperatures a gas will be less soluble in a liquid (given a constant pressure). Henry's law is of importance when considering the way inhaled anesthetic vapours and gases behave physiologically (see below).

Dalton's Law

Dalton's law states that the pressure of a gas in a mixture of gases is independent of the pressure of the other gases in the mixture. Alternatively, Dalton's law can be expressed as 'the total pressure of a mixture of gases is equal to the sum of the partial pressures of the constituent gases'. Dalton's law can be explained by the fact that in a mixture of gases the molecules are so far apart from one another, that each gas behaves as though the others were not present. As mentioned above, Dalton's Law explains why vapour pressure is not affected by ambient pressure.

Imperfections in the gas laws

In reality, the gas laws described above are not always true and they refer to a theoretical 'ideal' gas. However in reality, these concepts generally hold true and, as long as correction factors used, the gas laws have practical applications. Note that the gas laws are only accurate when applied to gases above their critical temperature.

APPLICATION TO ANAESTHETIC GASES AND VAPOURS

Anaesthetic gases are supplied in cylinders and via pipelines from the central gas supply in each hospital. Each cylinder is painted a colour according to the gas it contains. Conventions regarding cylinder colour coding vary from country to country and the colour of a cylinder should never be relied on as the sole guide to the contents of the cylinder - always read the label. In Europe, standard EN 1089-3¹ is currently being implemented, the aim being to increase conformity and hopefully safety between different countries. According to EN 1089-3 the colour of the *cylinder shoulder* is the only part used to identify the gas and the colour of the body may vary between manufacturers. Cylinder shoulder colours are given in Table 2. Carbon dioxide is currently rarely used in anaesthesia, but cylinders containing carbon dioxide may still be encountered in medical settings and in examinations. Cylinders should be tested by the manufacturers at regular intervals, with pressure testing on all cylinders and tensile, flattening, bend and impact testing on a sample of one cylinder in every hundred.

Gas	Cylinder colour
Oxygen	White shoulder
Nitrous Oxide	Blue shoulder
Carbon Dioxide	Grey shoulder
Helium	Brown shoulder
Medical Air	Black and white checked shoulder
Heliox	Brown and white checked shoulder
Entonox	Blue and white checked shoulder

Table 2. European cylinder colour coding

Individual medical gases are described in more detail below.

Oxygen

Oxygen has a boiling point of -183°C and a critical temperature of -119°C , which means that at room temperature it is above its critical temperature and always exists as a gas, obeying the gas laws. The importance of this is that Boyle's law can be applied to oxygen, which means that the reading on the pressure gauge of an oxygen cylinder gives a true indication of the volume remaining. However, inaccuracies may arise in this respect if large alterations in ambient temperature occur.

Oxygen manufacture and storage

Oxygen can be stored under pressure in cylinders made of molybdenum steel. Cylinders may be combined to form a bank attached to a manifold. The advantages of combining large cylinders into a bank include a reduction in cost, transportation and constant

change of exhausted cylinders. Oxygen cylinders come in various sizes, the most common used in operating theatres being sizes D and E. The filling pressures and volumes of various oxygen cylinders are given in Table 3.

O ₂ cylinder	Water capacity (l)	Filling pressure (bar)	O ₂ volume at 1bar (l)
C	1.20	137	170
D	2.32	137	340
E	4.68	137	680
F	9.43	137	1360

Table 3. Oxygen (O₂) cylinders. The values given are for full cylinders at 15°C as per BOC Medical data.² These may vary between manufacturers and with fluctuations in ambient temperature and pressure

As described above, oxygen has to be cooled to below -118°C to change to a liquid. When the gas changes form to a liquid, it occupies a much smaller volume. Therefore when a small volume of liquid oxygen is warmed it will make a very large volume of oxygen gas. As an alternative to cylinders, oxygen can be stored as a liquid in a specialised container. In the liquid form, a very large quantity of oxygen can be transported or stored in a low volume, although there are problems in keeping the liquid cold as explained below.

Vacuum insulated evaporator (VIE)

A VIE is a container designed to store liquid oxygen. It has to be designed to allow the liquid oxygen inside to remain very cold. It consists of two layers, where the outer carbon steel shell is separated by a vacuum from an inner stainless steel shell, which contains the oxygen (Figure 3). The oxygen temperature inside is about -170°C and the container is pressurised to 10.5bar. Gaseous oxygen above the liquid is passed through the superheater to raise the temperature to ambient (outside) levels. It then flows into the hospital pipeline system giving a continuous supply of piped oxygen to outlets on the wards and in theatre. Heat is always able to get into the container and provides the energy to evaporate the liquid oxygen, changing it into oxygen gas which is continuously drawn off into the pipeline system. This escape of gas into the pipeline system prevents the pressure inside the container from rising. If the pressure rises too high (above 17bar), oxygen is allowed to escape via a safety valve into the atmosphere.

In contrast, if the pressure inside the container falls because of heavy demand in the hospital for oxygen, liquid oxygen can be withdrawn, passed through the evaporator and returned to the VIE in the gaseous form to restore the pressure. The amount of oxygen available in the container is estimated by weighing the container with an in-built device. The VIE system is used in large hospitals which have a pipeline system, and where liquid oxygen can be supplied by road tanker.

Nitrous Oxide

The boiling point of nitrous oxide is -88.6°C and the critical temperature is $+36^{\circ}\text{C}$. Since in most countries nitrous oxide is below its critical temperature at room temperature, it exists as a vapour in equilibrium with its liquid phase and is dependent upon the pressure applied to it. Therefore, under normal circumstances, the gas laws do not apply to nitrous oxide.

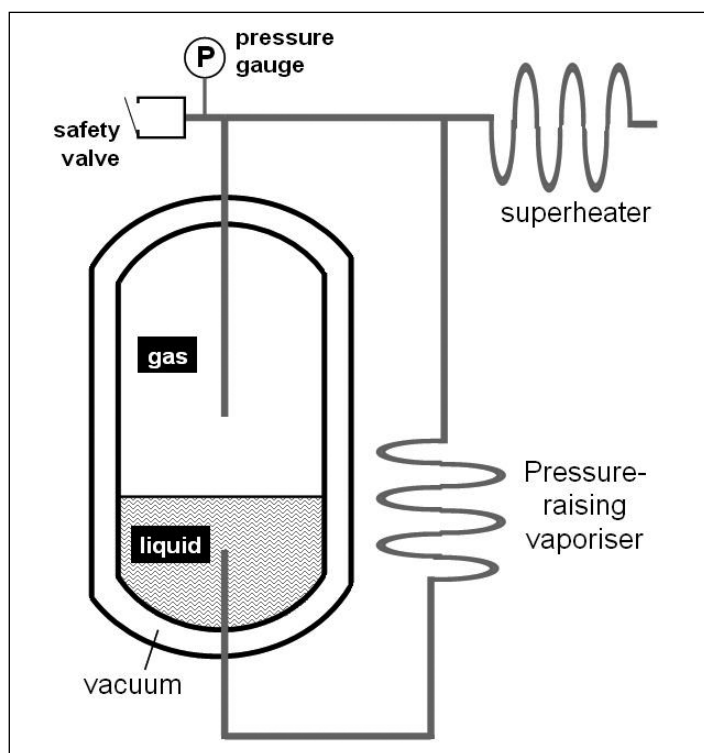


Figure 3. Vacuum insulated evaporator. Note the oxygen gas above the liquid oxygen. The gas enters the pipeline system at the top and if large quantities of oxygen are needed, liquid is drawn off at the bottom of the VIE and passes through the evaporator and the gas then enters the pipeline system

Unlike oxygen, the pressure gauge on a nitrous oxide cylinder tells you nothing about the amount of nitrous oxide remaining in the cylinder - it always reads around 52bar at room temperature. As shown in Figure 4, 52bar is the pressure at which nitrous oxide liquifies at 20°C and this is also the vapour pressure of nitrous oxide at 20°C. In a cylinder at room temperature, nitrous oxide exists as a liquid in equilibrium with its vapour. As vapour is drawn off, nitrous oxide moves from the liquid to the vapour phase, maintaining the equilibrium between the phases, and the vapour pressure within the cylinder. As nitrous is drawn off there is a small transient fall in vapour pressure, but once turned off, the contents will return to equilibrium and the vapour pressure is re-established at approximately 52bar.

To determine how much nitrous oxide is left in a cylinder it must be weighed, the weight of the empty cylinder subtracted, and then the number of moles of nitrous oxide in the cylinder calculated using Avagadro's number (see Box 1).

The ideal gas law can then be used to calculate the approximate volume of gas remaining. Given this, it is easy to understand why nitrous oxide cylinders are not filled to a given pressure. A value called the *filling ratio* is used instead. This is the ratio of the weight of the cylinder filled with nitrous oxide to the weight of the cylinder when filled with water. In the UK the filling ratio of nitrous oxide cylinders is 0.75, however this is reduced to 0.67 in hotter climates.

Entonox

Entonox is the trade-name from BOC Medical for 50% oxygen and 50% nitrous oxide. Entonox is supplied in cylinders at 137bar at

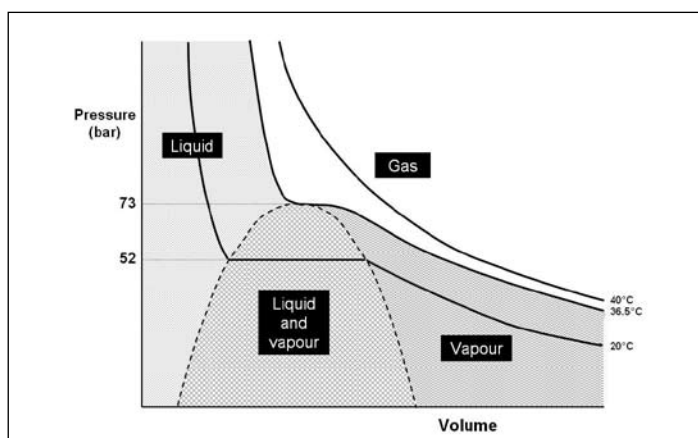


Figure 4. Nitrous oxide isotherms. Isotherms join points on the pressure volume graph that exist at the same temperature. Note that A - at 40°C nitrous oxide obeys Boyle's law; B - points 1 and 2 correspond to a nitrous oxide cylinder. A constant pressure is maintained despite alterations in volume

Avagadro's number (L):

The number of fundamental particles in 1mole of any substance is equal to the number of atoms in 12g of pure ^{12}C .

The number is approximately $6 \times 10^{23} \text{ mol}^{-1}$.

In practice this can be used to calculate the number of moles of a substance if the total weight of the substance in question, and the molecular weight of the fundamental particle, is known:

$$\text{Number of moles} = \frac{\text{mass of substance (g)}}{\text{molecular or atomic mass}}$$

15°C or delivered via pipelines in the hospital at 4bar in the UK. For any mixture of gases, such as Entonox, the critical temperature is termed the *pseudocritical temperature*. In anaesthesia, however, the term *pseudocritical temperature* is almost always used to describe the temperature at which Entonox starts to separate (or 'lamine') into its constituent parts. Strictly speaking this temperature should be termed the 'laminating temperature', but *pseudocritical temperature* is a more widely used term.

As described above, at temperatures below the pseudocritical temperature it is possible for the individual gases in a mixture of Entonox to separate out into liquids. In practice this means that the nitrous oxide component of the entonox starts to move into the liquid phase. The pseudocritical temperature of entonox is approximately -6°C, allowing for slight variation due to small differences in cylinder pressure. At, or below, this temperature the concentration of the oxygen in the gaseous phase increases as nitrous oxide moves into the liquid phase. This has clinical importance. Although the inspired gas will initially contain a high concentration of oxygen, this gas is gradually exhausted, at which point the nitrous oxide will return to the gas phase, resulting in delivery of a hypoxic gas mixture of pure nitrous oxide. One design feature of Entonox cylinders to try and prevent this happening is that the tip of the pipe drawing the gas from the inside of the cylinder is generally placed near the bottom, close to the liquid surface. This means that if the nitrous oxide starts to liquefy, then an 'underwater seal' should form, preventing further gas

from being drawn. If there is a possibility of separation occurring, the manufacturers recommend that prior to use cylinders should be stored horizontally for 24hrs at a temperature above 10°C or alternatively, warmed to 10°C for two hours (or body temperature for 5 minutes) and then completely inverted 3 times.³

The gases in an Entonox mixture do not behave in a way that could be predicted from their individual properties and the pseudocritical temperature of Entonox alters with ambient pressure in a non-linear fashion. The pseudocritical temperature is highest at 117bar (-5.5°C) and decreases at pressures either side of this. In the UK, the pipeline supply pressure of 4bar gives a pseudocritical temperature around -30°C.

Heliox

Heliox is a mixture of oxygen and helium. The percentage of oxygen in the mixture can vary but may be as low as 21% and not higher than 50%. Heliox is useful in patients with upper airway obstruction but evidence of its clinical effectiveness is lacking.⁴ Theoretically patients with airway obstruction have a greater amount of turbulent compared to laminar air flow within their airways. Helium has a lower density than oxygen (and nitrogen) and this may increase airway gas flow when flow is turbulent. The density of a gas has no effect on flow when the flow is laminar - see Box 2.

The **Hagen-Poiseuille** equation for laminar flow through a tube:

$$\text{Flow, } Q = \frac{\pi \Delta P r^4}{8 \eta l}$$

Where ΔP = pressure differential, η = viscosity, l = length of tube, r = radius of tube

APPLICATION TO VOLATILE ANAESTHETIC AGENTS

The inhaled anaesthetic agents are also known as volatile anaesthetic agents because that they all have relatively high vapour pressures at room temperature. A distinction can be made between the volatile anaesthetic agents, such as isoflourane and halothane, which are usually a liquid at room temperature and gaseous anaesthetic agents, such as nitrous oxide and xenon, which are gases at room temperature. This section deals primarily with the former.

Volatile anaesthetic agents exert their effect according to the partial pressure of the agent in the blood - the greater the partial pressure, the greater the anaesthetic effect. According to Henry's law the partial pressure of anaesthetic agent dissolved in the blood is proportional to the partial pressure exerted by the anaesthetic vapour in the alveoli. Application of Dalton's law tells us that the partial pressure exerted by the anaesthetic vapour in the alveoli is independent of the other gases present in the mixture. So, the factors that alter the pressure exerted by the anaesthetic vapour are the vapour pressure itself and the amount of agent carried into the alveoli per unit volume (that is dictated by the concentration of anaesthetic vapour in the gas mixture).

Vaporisers

A vaporiser is a tool that accurately adjusts the amount of anaesthetic vapour added to the inhaled gas mixture and, in doing so, determines the concentration of vapour in the alveoli. A vaporiser does not generally alter the vapour pressure of an anaesthetic agent, and this remains relatively constant. The partial pressure of an anaesthetic agent in the alveoli increases when a vaporiser is turned up simply because it is at a higher concentration in the gas mix, and so its *partial pressure* increases. One variable that can alter the anaesthetic vapour pressure in a vaporiser is temperature.

When vapour is drawn off, evaporation of the liquid part of the anaesthetic agent takes place to maintain the equilibrium. This is an endothermic reaction that cools the liquid as the *latent heat of vaporization* comes from the liquid in the form of heat energy. The anaesthetic vapour pressure falls with the potential for delivery of a lower concentration of anaesthetic vapour and lightening of anaesthesia. Modern vaporisers incorporate various mechanisms to compensate for any drops in temperature to overcome this problem.

Altitude

A favorite examiner's question is 'What adjustment do you need to make to your vaporiser settings if you are anaesthetising a patient at altitude?' Two concepts answer this question. First, anaesthetic depth is controlled by altering the partial pressure of anaesthetic agent in the alveolus (Henry's law), and second, only two factors affect the partial pressure - the vapour pressure of the anaesthetic agent in the vaporiser and the concentration of this vapour in the inhaled gas mixture. Vapour pressure does not change with ambient pressure, so remains constant at altitude. The concentration of vapour in the inhaled gas mixture depends on the ratio of gas diverted through the vaporiser compared to the amount bypassing the vaporiser (*the splitting ratio*). Because this depends on a ratio it also does not change at altitude. So, the answer is that no change needs to be made to vaporiser settings at altitude. For completeness, however, you could point out that ambient temperatures are generally lower at altitude, and that this might affect the efficiency of the temperature compensation mechanisms of a vaporiser.

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Vaporisers

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Summary

This article should be read in conjunction with the previous article, 'Gases and vapours'. Several areas and concepts are duplicated but are retained for the benefit of an alternative explanation. Full coverage of the features of all vaporisers is clearly not possible, however the common underlying principles of their function are demonstrated using examples of widely-used devices. A clear understanding of the uses and pitfalls of vaporisers is essential for their safe clinical use.

DEFINITIONS

Definitions of the terms vapour, gas, and critical temperature can be found in the previous article, *Gases and vapours*.

'Volatile anaesthetic agents' are liquid at room temperature and atmospheric pressure. Liquids consist of molecules which are in constant motion and have a mutual attraction to each other. If the surface of the liquid is exposed to air, or any other gas, some molecules escape from the surface when their energy is more than the energy of the attraction to the other molecules. This is the process of evaporation which is increased with heating. Volatile agents are able to evaporate easily and do not require heating to liberate the vapour. If we pour a volatile agent into a confined space, such as a jar with a lid on it, over time the vapour liberated from the liquid accumulates in the space available in the jar. As it accumulates the molecules move randomly and exert a pressure. In the enclosed jar some of the molecules that have escaped will collide with the surface of the liquid and re-enter the liquid phase. Ultimately the process reaches equilibrium. At that point there are equal numbers of molecules leaving and returning to the liquid. The saturated vapour pressure

(SVP) is the pressure exerted by the molecules in the vapour at the point of equilibrium. If the liquid is not contained in a confined space the process of evaporation continues until all of the agent has converted from liquid to vapour and dissipated into the surrounding atmosphere. Leave the lid off a bottle of halothane and there won't be any left an hour or two later!

Saturated vapour pressure

As explained above, the SVP is defined as the pressure exerted by the vapour in equilibrium with the liquid phase. It is dependent on the agent concerned, and its temperature, nothing else. When SVP is equal to atmospheric pressure, the liquid boils, i.e. pure water at sea level at 100°C has an SVP of 101.3kPa (760mmHg, one atmosphere).

Latent heat of vaporisation

Energy is needed to convert a substance from a liquid state into vapour or gas. The latent heat of vaporisation is defined as the amount of energy required to convert 1g of liquid into vapour without a change in temperature. The more volatile the liquid is, the less energy required. The latent heat of vaporisation is expressed as kJ.g⁻¹, or kJ.mol⁻¹, considering that different agents have different

Table 1. Boiling points and SVPs of commonly available volatile anaesthetics

Agent	Boiling point (°C, at one atmosphere)	Saturated vapour pressure at 20°C (mmHg)	Saturated vapour pressure at 20°C (kPa)	Latent heat of vaporisation (kJ.mol ⁻¹)
Halothane	50.2	241	32.3	28.9
Ether	34.6	442	58.2	27.6
Enflurane	56.5	175	23.3	32.3
Isoflurane	48.5	240	33.2	-
Trichloroethylene	86.7	58	7.6	31
Methoxyflurane	104.7	22.5	3.0	33.9
Sevoflurane	58.5	60	22.7	-
Desflurane	23.5	678	89.2	-

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molecular weights. If the energy is not supplied from an external source then it must be taken from within the liquid itself. This causes the liquid to cool (heat energy is used). Drop some halothane or ether on your forearm and feel it cool as it evaporates, taking heat from your skin. This is also the rationale behind using ethyl chloride to 'freeze' the skin as a topical anaesthetic.

Volatility

This is the common term which links latent heat of vaporisation and saturated vapour pressure. The more 'volatile' an agent, the less energy required to convert liquid into vapour, and the more pressure exerted by that vapour at a given temperature. It is agent and temperature dependent. Trichloroethylene, for instance, is less volatile than ether.

Examples of points made so far

Take the lid off a tin of paint and you will smell its vapour. The smell is strong at first, because the vapour is concentrated in the tin. It is in equilibrium with the paint. We say it is 'saturated'. The tin has been closed for a long time, and the saturated vapour pressure is the point where equal numbers of paint molecules are becoming vapour, or returning into the liquid (paint). Very soon after removing the lid the smell disappears. The vapour has diffused away in the atmosphere, and because the paint is poorly volatile, very little is liberated from the paint. If left open, the paint becomes solid before it evaporates.

Compare this with petrol, which is more volatile. If the lid is left off the tin the smell continues to be strong as large amounts of vapour are being released from the petrol. Within a short time there is no petrol left in the tin, it has all become vapour and dispersed into the atmosphere. If the petrol can was filled on a mild day, on a hotter day the tin will hiss out as you open the lid, and on a colder day the tin sucks air in. The SVP is higher on hot days, and lower on cold days, because it is dependent on temperature.

VAPORISERS

Vaporisers are devices designed to deliver safe concentrations of volatile anaesthetic vapour to a patient's breathing circuit. The volatile agent goes into the vaporiser in liquid form, and comes out as a vapour, at precisely the concentration desired by the anaesthetist. There are features common to most vaporisers, such as the variable bypass channel, and the vaporising chamber, but most vaporisers are agent specific, meaning their dimensions are based on the characteristics of one volatile agent, and they only perform reliably if used with that agent.

Most classification systems are academic or cumbersome, and have reducing clinical relevance the more comprehensive they become. In practical terms it is important to be able to discriminate between different characteristics that dictate how they are used, or how they may be expected to perform. Develop your own system. In terms of practicalities, the following distinctions can be made:

Drawover versus plenum

Drawover is when carrier gas is pulled through the vaporiser by a decrease in downstream pressure, and plenum is when carrier gas is pushed through the vaporiser at higher than ambient pressure.

Agent specific versus multi-agent

Determines what agent can be used in them.

Temperature compensated?

Indicates a consistency of performance with time, over a range of operating temperatures, versus a need to adjust dial settings according to decreasing output as vapour cools as it evaporates.

Flow stabilised?

At what flow rates will the output be reliable?

Flow resistance?

How much effort is required to draw, or push, carrier gas through the vaporiser?

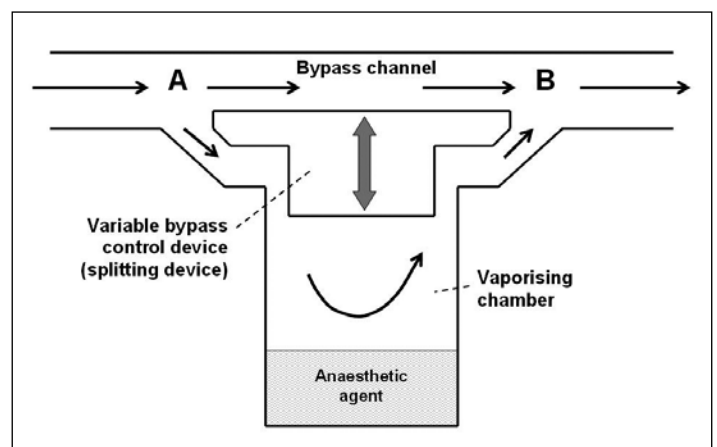


Figure 1. Basic elements of a vaporiser. The carrier gas enters the inlet. At point A the gas is split into two streams, one passing along the bypass channel, the other directed into the vaporising chamber. The amount of flow into the vaporising chamber is controlled by the 'splitting device'. In the vaporising chamber the gas is saturated with anaesthetic vapour. At point B vapour mixes with the bypass gas and then exits via the outlet

Combining some of the above characteristics, vaporisers can broadly be classified into two main categories, as follows

1. Drawover or plenum
2. Calibrated or uncalibrated

Calibration is the term used to describe the precision of performance within a specified range of conditions. Manufacturers supply data to show how well output matches ideal performance. Giving a hypothetical example a vaporiser may be calibrated to perform within $\pm 10\%$ of the dial setting, at flow rates between 2 and 10 litres per minute. Outside these limits the performance is less reliable. The structural methods used to improve calibration are outlined below.

VAPORISER STRUCTURE

The basic components are the vapour chamber and the flow-splitting device. In all situations other than open-drop anaesthesia the vapour needs to be delivered to the patient in a carrier gas passing along a circuit. Volatile agents cannot just be poured in because their SVP is too high, and the final concentration would be too great, causing overdose. The vaporiser is used to add a safe, predictable and controlled concentration, and a small percentage, into the anaesthetic circuit.

Most vaporisers use the method of splitting the carrier gas into two streams as it passes through. One stream passes into the vaporising chamber, and the other passes by (by-passes) directly into the anaesthetic circuit without contacting the vapour. The ratio of the gas flows in each stream is called the splitting ratio. The splitting ratio is principally controlled by the concentration dial, allowing the anaesthetist to vary the output according to the desired amount.

The exception to all of the above is the 'copper kettle' which is a measured flow vaporiser, as opposed to variable bypass. It will not be considered further here.

Downstream from the vaporiser the streams of vapour-laden and vapour-free gas mix in the anaesthetic circuit. In calibrating the vaporiser, the manufacturer assumes that all carrier gas passing through the vaporising chamber becomes saturated with anaesthetic vapour, which has a known concentration. The desired output can then be produced by altering the splitting ratio which determines the dilution of the vapour-laden gas with fresh gas to give a final concentration in the desired clinical range. It is vital therefore that the vaporising chamber produces a saturated vapour. This is achieved by the following devices.

- **Wicks** are used to increase the surface area of the liquid/gas interface where vaporisation occurs, ensuring saturation of the carrier gas as it passes through (see Figure 2). This is crucial to the determination of output. Without wicks the vapour concentration will not achieve SVP, because too little vapour can be liberated from the small interface in unit time, as the carrier gas passes through (taking vapour away). Performance will fall with time. One example of a wick-less vaporiser is the Goldman.



Figure 2. The wick system of an Oxford miniature vaporiser (OMV) consists of metallic mesh

- **Baffles** are simple plates or channels that encouraging mixing of carrier gas with vapour, ensuring saturation before the carrier gas returns to the anaesthetic circuit.
- **Temperature compensation devices.** Since SVP is dependent on temperature, the output of the vaporiser will be different at different temperatures, if the splitting ratio remains fixed. As temperature falls the SVP falls, so the concentration leaving the vaporising chamber will fall and thus contribute less vapour

to the carrier gas as it passes through, and the final output (%) will fall, unless the splitting ratio alters to accommodate the change. This is exactly what the manufacturers have introduced, and it is termed temperature compensation. There are various designs which achieve this, but the common element is an indirect increase in the splitting ratio with a fall in temperature, without any alteration of the dial setting, by outflow modification (see Figure 3).

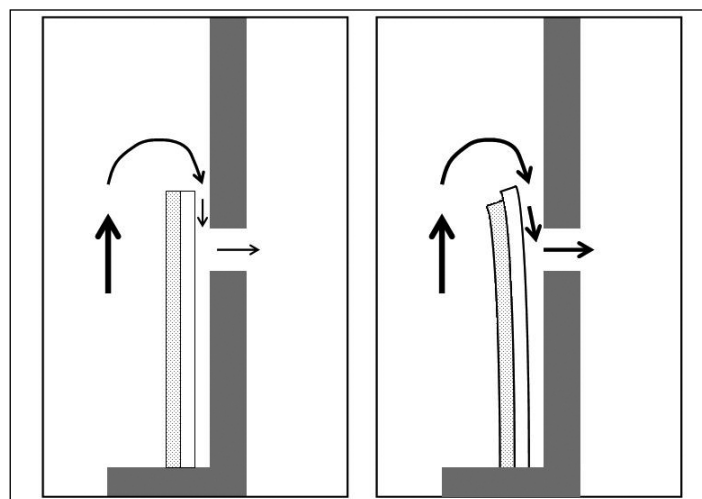


Figure 3. Bimetallic strips. The two metals expand or contract in response to temperature, but at different rates such that the strip is forced to bend away from the aperture when the system cools, allowing more vapour out, and compensating for the decrease in vaporisation at the lower temperature

The aim of the calibrated vaporiser is the provision of a steady, predictable output that correlates with the dial setting in a wide range of environmental conditions. To offset the cooling effect of vaporisation (latent heat), vaporisers are built from conductive materials which can donate heat energy to the liquid. A large mass of such material is referred to as a heat sink. Examples include the water bath of the EMO, and the thick copper base of the Tec vaporisers. Improvised heat-sinks can be made, such as wrapping a warm, wet towel around a Boyle's bottle when using ether. Further temperature compensation (flow compensation) occurs by internal adjustments in the splitting ratio when temperature falls or rises. The commonest method for achieving this is with a bimetallic strip (Tec series) in which two conjoined, dissimilar metals expand or contract at different rates as temperature varies (Figure 3), thus opening or closing the output aperture of the vapour chamber. An alternative system is the ether-filled-bellows (Penlon) attached to a spindle valve (Figure 6). The bellows change size with temperature changes, altering the relationship of the spindle to the seat, with an effect on the output, and therefore the splitting ratio. As vapour cools the bellows shrink, and the aperture increases, allowing a greater 'output'.

DRAWOVER VAPORISERS

The basic elements are:

- Low internal resistance to gas flow.
- Gas is drawn through the vaporiser into the anaesthetic circuit only in inspiration, or by the use of a self inflating bag or bellows,

therefore flow is not constant (peak inspiratory flow rates 30-60L.min⁻¹), but more 'pulsatile' in nature.

- Do not require a pressurised gas supply

Goldman halothane vaporiser (similar to McKesson and Rowbotham - Trilene)

- Adapted from Leyland fuel pump.
- Very simple splitting device.
- No temperature compensation - therefore output varies with temperature and decreases during use, as the temperature falls.
- With halothane the maximum output is 3% because of the small vapour chamber and absence of wicks.
- It can be used in a circle system, but needs vigilance as the output varies dramatically depending on whether the patient is spontaneously breathing (lower), or ventilated by positive pressure (higher). Circle flow rates also influence output. This area is too complex to tackle within this broad article.

Oxford Miniature Vaporiser (OMV) - drawover or plenum (Figure 5)

- Portable.
- Multi-agent.
- Easily cleaned and serviced.
- Wire-gauze wick.
- No temperature compensation.
- Small heat sink containing glycol.



Figure 5. The Oxford miniature vaporiser (OMV)

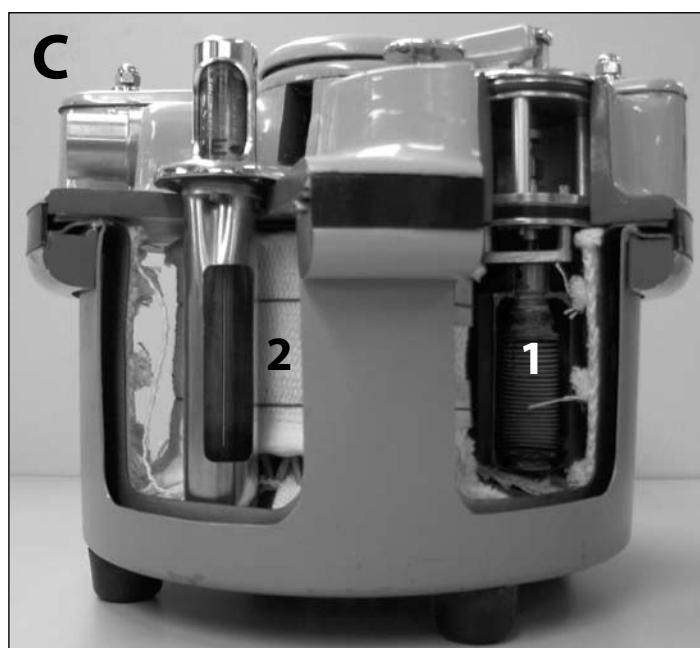
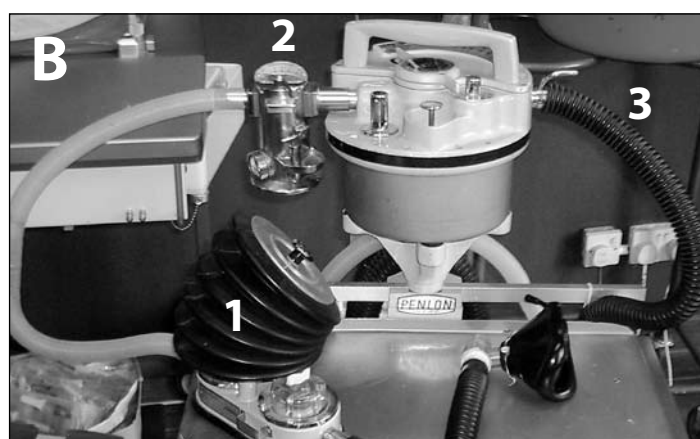


Figure 6. (A) The EMO ether vaporiser, (B) EMO in a drawover circuit with Oxford inflating bellows (1), an OMV in series (2) and a patient breathing system (3), (C) Cut-away EMO showing temperature compensating bellows (1) and wick system (2)

EMO ether inhaler (Epstein, Macintosh, Oxford)

- Robust.
- Water-bath heat sink.
- Ether bellows temperature compensator.
- Level indicator.

Open drop techniques (ether and chloroform) - e.g. Schimmelbusch mask and Ogston's inhaler

- Drop rate gives inspired concentration.
- Number of layers of gauze or lint important (wick).
- Freezing may occur (latent heat).
- Eye protection needs to be considered (freezing).

PLENUM VAPORISERS

Plenum is a term derived from Latin, and means 'full'. It is the opposite to vacuum ('empty'). In air conditioning terminology it applies to air that is forced in, cleaned and temperature adjusted. Plenum vaporisers are designed for use with continuous flow of pressurised gas and have high internal resistance. Modern versions are universally agent specific, and referred to as flow stabilised, i.e. they perform equally well over a large range of fresh gas flows, usually $\pm 20\%$ accurate between $0.5\text{--}10\text{ l}\cdot\text{min}^{-1}$.

Boyle's bottle

This vaporiser is neither temperature compensated nor agent specific, although designed for use with ether. When in the down position, the cowl over the U-tube forces gas to bubble through ether, increasing output by increasing the gas/liquid interface. There is the potential for a surge of high concentration of ether when first turned on, as the chamber contains ether at SVP. While standing idle the equilibrated SVP of ether is 60kPa - this constitutes a concentration of 59.2% $[(60/101.3) \times 100]$.

The vaporiser cools dramatically in use, with a drastic decrease in output with the possibility of the patient lightening or awakening, unless counteracted by an external heat sink (hot towel or warm water bath) and further depression of the cowl into the ether liquid. They tend to need frequent refilling while in use.

Tec 2 (Ohmeda) halothane vaporiser

- Temperature compensated.
- Bimetallic strip.
- Series of wicks.
- Metal heat sink.

Many newer models of vaporisers exist and have refined performances, particularly for low flow rates, to facilitate low flow circle anaesthesia. They are characterised by larger wicks, output resistance to minimise the 'pumping effect' and metal heat sinks.

Pumping effect (increased vapour output at low flows)

This effect applies to plenum vaporisers, especially at low flow rates with IPPV, when back pressure is exerted on the vaporiser. Typically

this happens when manually assisted or ventilator controlled ventilation is being used.

The pressure in the anaesthetic circuit and vapour chamber rises during inspiration. This drives some saturated vapour back from the vapour chamber into the inlet path, which spills into the by-pass carrier gas when the pressure falls during expiration. The by-pass is thus contaminated and will result in an inaccurate output concentration. Designers have minimized the effect by increasing the internal resistance which reduces the back flow into the vaporising chamber. Other measures to prevent it include an outlet 'non-return valve' (resistance) which maintains constant pressure in the vapour chamber, and long high-resistance inlet pathways (Drager).

Pressure effect (decreased vapour output at high flows)

This effect is seen in plenum vaporisers, at high flow rates during IPPV, and is of minor significance. Positive pressure compresses the carrier gas, thus concentrating it. When the pressure is released (expiration), volume increases, the gas density falls and the vapour concentration also falls.

VAPORISER SAFETY

To enhance the safety aspects of using volatile agents the following adaptations have become commonplace:

- Keyed filling devices reducing the likelihood of filling with the wrong agent.
- Agent level indicators.
- Stable mounting brackets to prevent tipping and spillage.
- Correct placement in circuit:
 - Plenum downstream from rotameters, upstream of oxygen,
 - Draw-over upstream from self inflating bag/bellows.
- Interlock devices to stop the concurrent use of two vaporisers in series, preventing contamination from upstream to downstream vaporiser. If an interlock device is fitted, a small metal rod protrudes from the side of the vaporiser, towards the rear. When the dial is turned on, the rod sticks out further. If two interlock compatible vaporisers are mounted side by side then this prevents the second vaporiser from being switched on as the rods are in contact, and the second dial will not turn.
- Correct placement in series (if no interlock); the more volatile agents (highest SVP) should be placed downstream, as less volatile agents have lower splitting ratios and will create less contamination of downstream vaporisers if both are switched on. Halothane should be placed downstream to prevent thymol contamination of others vaporisers.
- Agent monitoring, checking that the circuit concentrations are adequate.

POTENTIAL MISADVENTURES

- **Overfilling** may have an unpredictable effect on output. Liquid agent may spill into the bypass and increase output dramatically, or conversely, reduced wick surface area may lead to reduced output.

If overfilled it is wise to drain the vaporiser to the recommended range as indicated by the agent indicator.

- **Crossed connection - reversed connection.** This will lead to unpredictable output. In the Tec series the manufacturers claim delivered concentration to be approximately double that dialled.
- **Tipping over** results in high output as the splitting device inlet is contaminated by liquid agent and bypass gas also collects vapour. The vaporiser should be flushed for 10 minutes at 10l.min⁻¹ before use, or left to stand overnight.
- **Incorrect filling** (wrong agent). Output will not match dial setting and may be grossly excessive (overdose), or inadequate (intraoperative awareness) if used by an unsuspecting anaesthetist.

HYPOBARIC AND HYPERBARIC ENVIRONMENTS

In these situations the output from the vaporiser can alter. SVP

remains unchanged as it is only temperature dependent, but there is a change in ambient pressure relative to SVP. This then alters the output concentration (%). However the partial pressure of the vapour does not change. Since the partial pressure of the volatile agent is the important factor in causing anaesthesia, there is no reason to vary the vaporiser settings from normobaric use. If using agent monitoring, however, the MAC value in % will be inappropriate and should not be relied upon - use kPa or mmHg as a guide to the partial pressure instead. Pressure reversal of anaesthesia is not a clinically significant phenomenon in therapeutic hyperbaric chamber pressures.

CONCLUSION

It is impossible to cover all aspects of vaporiser function and performance, in all conditions, with all agents. Hopefully an understanding of the general principles involved will allow you to predict what is safe, unsafe, achievable, or impossible when confronted with clinical choices, or a need to modify the use of a vaporiser to suit your own particular needs.

Originally published in Anaesthesia Tutorial of the Week (2006)

The Physics of Flow

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Introduction

Flow is defined as the quantity of fluid (gas, liquid or vapour) that passes a point per unit time. A simple equation to represent this is:

$$\text{Flow (F)} = \frac{\text{Quantity (Q)}}{\text{Time (t)}}$$

Flow is sometimes written as ΔQ (rate of change of a quantity, mass or volume).

Due to the a quantity of different fluids that are given to our patients during a routine anaesthetic, flow is an important area of physics to understand.

Consider the following questions - the answers are contained within the following text.

1. Why are the scales on rotameters (flow meters) non uniform as the flow increases? Why are there different rotameters for different gases? See Figure 1.
2. Under what circumstances is the gas in Figure 2 useful, and why?
3. Will there be much difference in ventilating through a size 4 endotracheal tube compared to a size 8 endotracheal tube?

4. How much more fluid can be administered through a 14G cannula than a 22G cannula?

In order to answer these questions we need to understand the physical principles that govern flow.

Summary

This article covers the definition of flow, the different types of flow are there and the physical principles govern them. The Hagen-Poiseuille equation and its relevance to clinical anaesthetic practice are explained.

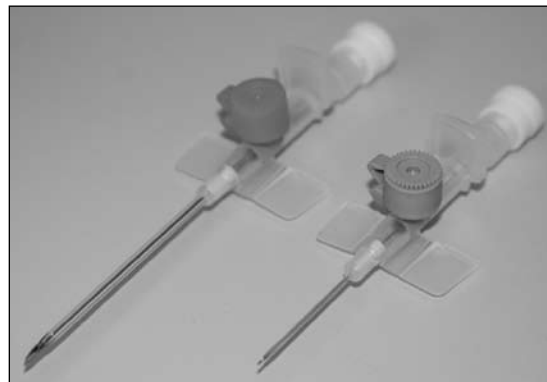


Figure 4. 22G and 14G cannulae

THE PHYSICS OF FLOW

Flow can be divided into two different types, laminar and turbulent. A number of different physical characteristics determine whether a fluid obeys the principles of one or the other.



Figure 1. Rotameters



Figure 2. Heliox



Figure 3. 4mm and 8mm internal diameter endotracheal tubes

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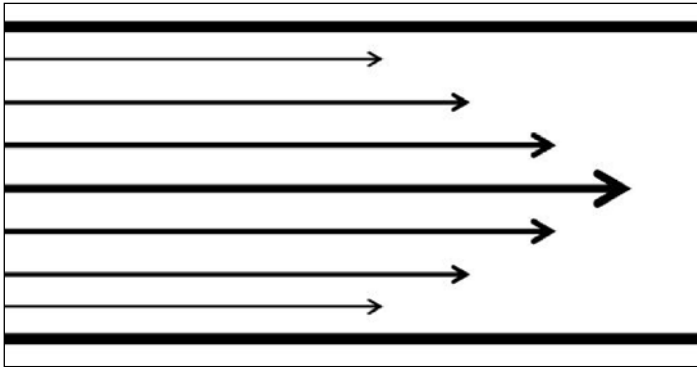


Figure 5. Diagrammatic representation of laminar flow

Laminar Flow

In laminar flow the molecules of the fluid can be imagined to be moving in numerous 'layers' or laminae as shown below.

Although all the molecules are moving in straight lines they are not all uniform in their velocity. If the mean velocity of the flow is v , then the molecules at the centre of the tube are moving at approximately $2v$ (twice the mean), while the molecules at the side of the tube are almost stationary. To help to understand this consider what happens when walking across a small river or stream; at the edge of the water by the river bank it does not feel like there is much movement of the water, whereas once you reach the middle the water is moving a lot faster. This is represented by the different lengths of the lines in the figure.

Flow is usually considered to be laminar when a fluid flows through a tube and the rate of flow is low. This is therefore the type of flow we would expect to see when a fluid flows through a cannula or a tracheal tube.

For flow to occur, there must be a pressure difference (ΔP) between the ends of a tube, and it can be demonstrated that ΔQ is directly proportional to ΔP ; in other words the greater the pressure difference, the greater the flow. (We squeeze a bag of IV fluid, to increase the pressure difference between the bag and the vein, so that the fluid is given more quickly.)

As fluid flows through tubes there is resistance between the fluid and vessel wall that opposes the flow. For any given system, this resistance is constant and can be expressed as:

$$\text{Resistance, } R \text{ (a constant)} = \frac{\Delta P}{\Delta Q}$$

(This can be compared with $V=IR$ in electrical physics).

Flow is affected by a number of other physical characteristics:

Tube diameter

If the diameter (d) of the tube is halved the flow through it reduces to one sixteenth. This means that flow is directly proportional to d^4 . Think about how much more rapidly fluid flows through a 16G than a 22G cannula.

Length

If the length (l) is doubled the flow is halved, therefore flow is inversely

proportional to the length of the tube. A central line is much longer than a cannula, and for the same diameter fluid flows more slowly. This demonstrates why a cannula is far better for giving fluid rapidly, during resuscitation.

Viscosity

This is a measure of the frictional forces between the 'layers' of a fluid described above - almost how 'sticky' the fluid is. As the viscosity increases the flow decreases proportionally, therefore flow and viscosity are inversely proportional. Viscosity is represented as η (the Greek letter, eta).

The Hagen-Poiseuille equation brings together all of the variables that determine flow along with a constant ($\pi/128$, that is derived theoretically).

$$\Delta Q = \frac{\pi P d^4}{128 \eta l}$$

where, P	=	pressure difference
ΔQ	=	flow
d	=	diameter of tube
η	=	viscosity
l	=	length of tube

Turbulent Flow

Not all fluid flow is laminar. Under certain physical conditions it becomes turbulent. When this happens, instead of the fluid moving in seemingly ordered layers, the molecules become more disorganised and begin to swirl with the formation of eddy currents, as shown in Figure 6.

Flow is less ordered and the eddy currents interfere with each other, increasing drag or resistance to flow. As a result, a greater energy input is required for a given flow rate, when flow is turbulent compared to when flow is laminar. This is best demonstrated by the fact that in turbulent flow, the flow rate is proportional to the square root of the pressure gradient, whereas in laminar flow, flow rate is directly proportional to the pressure gradient. This means that to double the flow, the pressure across the tube must be quadrupled.

When does turbulent flow occur?

Turbulent flow occurs when fluids flow at high velocity, in large diameter tubes and when the fluids are relatively dense. Also,

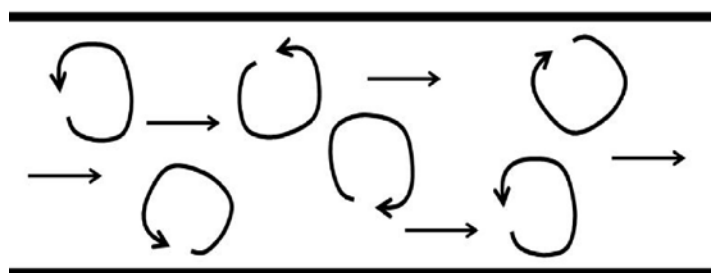


Figure 6. Diagrammatic representation of turbulent flow

decreasing the viscosity of a fluid leads to turbulent flow. The factors that determine when turbulent flow commences can be combined to form an equation which calculates the Reynolds number:

$$\text{Reynolds number} = \frac{v \rho d}{\eta}$$

where, v = velocity

ρ = density

d = diameter

η = viscosity

Measurements in tubes have shown that:

- when the Reynolds number is less than 2000 there is laminar flow,
- when the Reynolds number is 2000–4000 there is transitional flow i.e. a mixture of laminar and turbulent flow,
- when the Reynolds number is greater than 4000 flow will be turbulent.

Note that Reynolds number does not have any units associated with it - it is called a dimensionless number.

This equation shows that for a given fluid (of a certain density and viscosity), in a given tube, once a critical velocity is reached flow will become turbulent. The relevance of this within the body is that whenever a tube divides (e.g. bronchi, blood vessels) or there is a sharp bend or narrowing, velocity of the fluid increases, making turbulent flow likely to occur. Blood flow in the carotid artery becomes turbulent as it flows past an atheromatous plaque, hence the bruit heard with a stethoscope.

As we have seen, as the diameter of a tube increases, the Reynolds number increases. Eventually if the diameter of the tube increases enough, it will exceed the length of the tube. We then call this an orifice (see Figure 7). Generally speaking, provided that the critical velocity is not exceeded, flow through a tube is laminar and hence dependent on viscosity, whereas if it is through an orifice it is turbulent and dependent on density.

CLINICAL APPLICATIONS

Flowmeters

The flowmeters that are commonly used on anaesthetic machines are constant pressure, variable orifice flowmeters (the tradename is 'rotameter').

These are cone shaped tubes that contain a bobbin and are specific for each gas. The gas enters the bottom of the tube applying a force to the bobbin. The bobbin then moves up the tube until the force from below pushing it up is cancelled out by the gravitational force pulling the bobbin down. At this point it remains at that level and there is a constant pressure across the bobbin (pressure is force divided by area, with the area being constant).

At low flows, the bobbin is near the bottom of the tube and the gap between the bobbin and wall of the flowmeter acts like a tube (the diameter is small compared to the length). Gas flow is laminar and

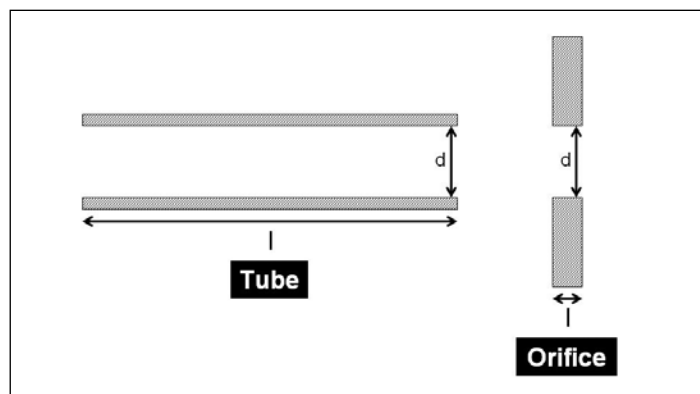


Figure 7. Difference between a tube and an orifice

hence the viscosity of the gas is important.

As flow rate increases, the bobbin rises up the flowmeter and the gap increases until it eventually acts like an orifice (the diameter becomes greater than the length). At this point the density of the gas affects its flow.

As flow changes from laminar to turbulent within the flowmeter:

- Individual gases have different densities and viscosities and therefore the flow past the bobbin will vary for each individual gas.
- The flow changes from being directly proportional to pressure to proportional to the square root of pressure and hence the graduations on the flowmeters are not uniform.

Heliox

Heliox is a mixture of 21% oxygen and 79% helium. Helium is an inert gas that is much less dense than nitrogen (which makes up 79% of air), therefore making heliox much less dense than air. In patients with upper airway obstruction, flow is through an orifice and hence more likely to be turbulent and dependent on the density of the gas passing through it. Therefore for a given pressure gradient (patient effort), there will be a greater flow of a low density gas (heliox) than a higher density gas (air). Although flow in the lower (smaller diameter) airways is considered to be laminar there may still be small areas of turbulence, giving some benefit, but not as much as that in the upper airways.

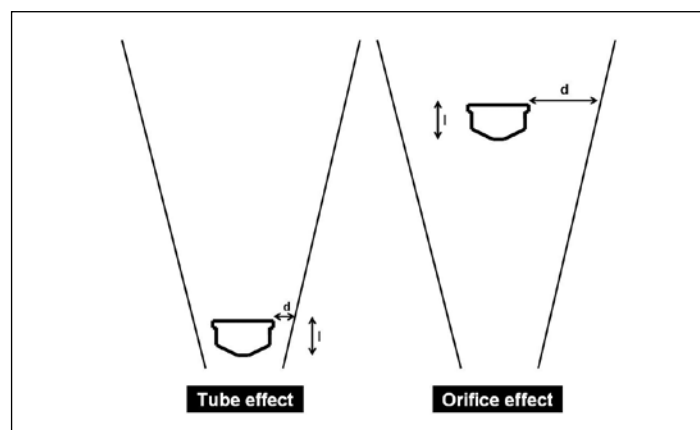


Figure 8. Diagrammatic representation of a rotameter, showing low flow on the left and high flow on the right

It must be noted that although flow with heliox increases in upper airway obstruction, it only contains 21% oxygen it may not be of benefit in the hypoxic patient.

Intravenous fluids

Intravenous fluids flow in a laminar fashion, therefore the rate of flow is determined by the Hagen-Poiseuille formula. This means that for a given fluid, with the same pressure applied to it, flow is greater through a shorter, wider cannula. This is why they are preferred in resuscitation to central cannulas that are long and small diameter.

To re-iterate, if the diameter of the tube is doubled the flow through it is increased by sixteen times.

Ventilation

The principles here are similar to those with the intravenous cannulae. Flow through a tracheal tube is laminar so the Hagen-Poiseuille

formula applies. If a smaller diameter tracheal tube is used, then flow will be significantly reduced as it is proportional to the fourth power of the diameter, unless the pressure gradient is increased (changing the tube from an 8mm to a 4mm may reduce flow by up to sixteen-fold!). This may be relatively easy to achieve with a mechanical ventilator, but if the patient is breathing spontaneously they will need to generate a much greater negative intrathoracic pressure. This will require the patient to work a lot harder and over time they will become exhausted, tidal and minute volume will be reduced and they will become hypercapnic. This is the reason why we don't allow patients to breathe spontaneously for any length of time through narrow tubes, such as those used for laryngeal surgery.

Also, look at the rest of the breathing circuit, acute angles at connections cause turbulent flow, thereby reducing flow for a given driving pressure, and unnecessary long circuits will reduce flow making the work of breathing greater.

Anaesthetic Breathing Systems

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DEFINITIONS

The function of breathing is to maintain a supply of oxygen to the lungs for oxygenation of the tissues, and to remove carbon dioxide from the body. When used for spontaneous ventilation, a breathing circuit must enable a patient to breathe satisfactorily without significantly increasing the work of breathing or the physiological deadspace. It must also conduct inhalational anaesthetic agents to the patient. The volume of gas inspired and expired with each breath is the *tidal volume* (normally 6-10ml.kg⁻¹), the total volume breathed in a minute is the *minute volume* and the volume of gas in the lungs at the end of normal expiration is the *functional residual capacity* (FRC).

The concentration of carbon dioxide in an exhaled breath varies with time; the first portion contains no carbon dioxide and comes from the upper respiratory tract where no gas exchange takes place (the anatomical dead space, about 2ml.kg⁻¹). The *anatomical dead space* is 25-35% of each tidal volume. As expiration continues, the concentration of carbon dioxide then rises rapidly to a plateau of about 5kPa (5% of the expired gas mixture) as alveolar gas is breathed out. The volume of alveolar gas expired per minute is called the alveolar minute ventilation. Any areas of lung that are ventilated with gas but are not perfused by blood cannot take part in gas exchange and represent the *alveolar dead space*. The total dead space in the patient (anatomical + alveolar) is the *physiological dead space*.

The term *rebreathing* implies that expired alveolar gas containing 5% carbon dioxide (and less oxygen than normal) is inspired as part of the next tidal volume. Anaesthetic circuits are designed to minimise rebreathing as it may lead to significant elevations in blood CO₂ levels. The amount of rebreathing that occurs with any particular anaesthetic breathing system depends on four factors:

1. The design of the individual breathing circuit.
2. The mode of ventilation (spontaneous or controlled).
3. The fresh gas flow rate.
4. The patient's respiratory pattern.

Circuits may eliminate rebreathing by:

1. Ensuring an adequate flow of fresh gas, that flushes the circuit clear of alveolar gas or,
2. Using soda lime, in a circle system, that absorbs the CO₂ so that low fresh gas flows may be used.

For each of the circuits described below, fresh gas flow rates that ensure minimal rebreathing are suggested.

THE MAPLESON CLASSIFICATION OF BREATHING SYSTEMS

A number of classifications exist and the one introduced in 1954 by Professor WW Mapleson is most commonly used in the UK (Figure 1). It does not however, include systems with carbon dioxide absorption.

The Mapleson A (Magill) system has been in use since the 1930s and remains an excellent system for spontaneous ventilation (Figure 2). Fresh gas enters the system at the fresh gas outlet of the anaesthesia machine. The expiratory valve (Heidbrink valve) is very close to the patient to reduce the dead space. The respiratory cycle has three phases during spontaneous breathing; inspiration, expiration and the expiratory pause. During inspiration gas is inhaled from the two litre reservoir (breathing) bag which partially collapses giving a visual confirmation that breathing is occurring.

During expiration the bag and tubing are initially refilled with a combination of exhaled dead space gas (containing no carbon dioxide) and fresh gas flowing from the anaesthetic machine. Once the bag is full, the pressure within the breathing system rises and the expiratory valve near the patient opens allowing the alveolar gas (containing carbon dioxide) to be vented from the system. During the expiratory pause more fresh gas enters the system driving any remaining alveolar gas back along the corrugated tubing and out through the valve. If the fresh gas flow is sufficiently high all the alveolar gas is vented from the circuit before the next inspiration and no rebreathing will take place. With careful adjustment the fresh gas flow can be reduced until there is only fresh gas and dead space gas in the breathing system at the start of inspiration.

Summary

The delivery systems which conduct anaesthetic gases from an anaesthetic machine to the patient are known as breathing systems or circuits. They are designed to allow either spontaneous respiration or intermittent positive pressure ventilation (IPPV) and consist of a reservoir bag, anaesthetic tubing, and (in most cases) a pressure relief valve. A number of mechanical ventilators include a specific breathing system, for example the Manley series. Other ventilators have been designed to operate with existing breathing systems, for example the Penlon Nuffield 200. This article focuses on the breathing systems used with plenum anaesthetic machines (those with a supply of pressurized gas); drawover apparatus will be described in a future article.

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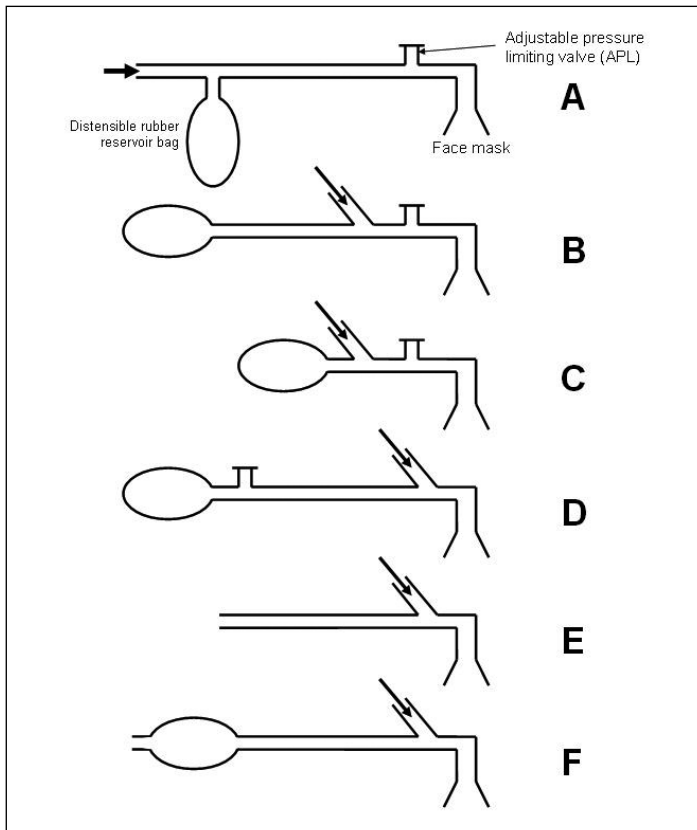


Figure 1. Mapleson classification of anaesthetic breathing systems. The arrows indicate entry of fresh gas to the system

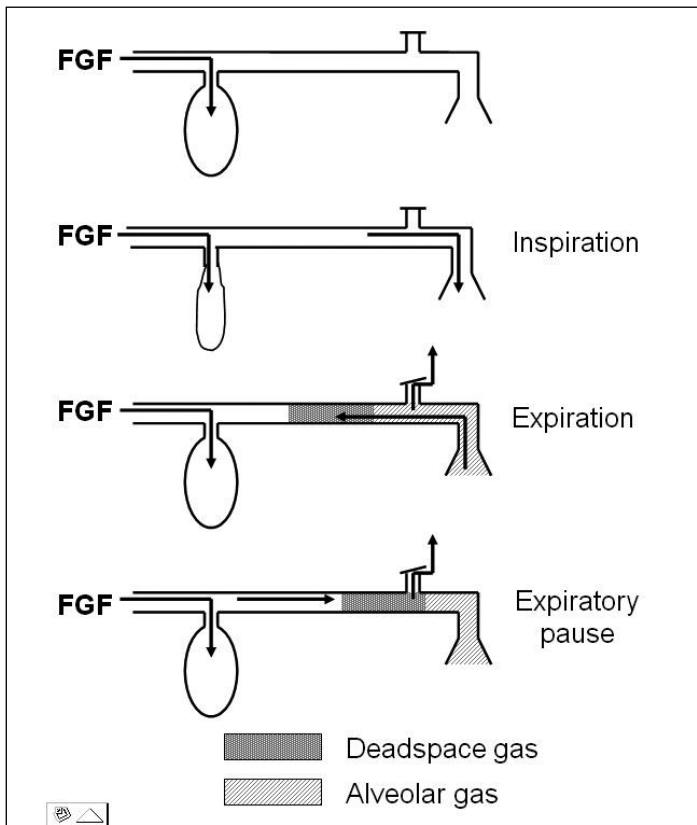


Figure 2. Mode of action of Mapleson A (Magill) breathing system during spontaneous ventilation

When the system is functioning correctly, without any leaks, a fresh gas flow (FGF) equal to the patient's alveolar minute ventilation is sufficient to prevent rebreathing. In practice however, a FGF closer to the patient's total minute ventilation (including dead space) is usually selected to provide a margin of safety. An adult's minute volume is approximately $80\text{ml.kg}^{-1}.\text{min}^{-1}$ and thus for a 75kg man a FGF of 6 litres per minute will prevent rebreathing. Where capnography is available this FGF can be titrated down, while watching for rebreathing, in order to limit gas use. This is an efficient system for spontaneously breathing patients, if carbon dioxide absorption is not available.

During controlled ventilation, the Magill circuit works in a different way and becomes wasteful and inefficient, requiring high fresh gas flows to prevent rebreathing (Figure 3). The inspiratory pressure is provided by the anaesthetist squeezing the reservoir bag after partly closing the expiratory valve next to the patient. During lung inflation some of the gas is vented from the circuit and at the end of inspiration the reservoir bag is less than half full. During expiration, dead space and alveolar gas pass down the system tubing and may reach the bag which will then contain some carbon dioxide. During the next inspiration, when the bag is squeezed, alveolar gas re-enters the patient's lungs followed by a mixture of fresh, dead space and alveolar gas. A FGF of two and a half times the patient's minute volume is required to vent enough alveolar gas to minimise rebreathing (a FGF of about

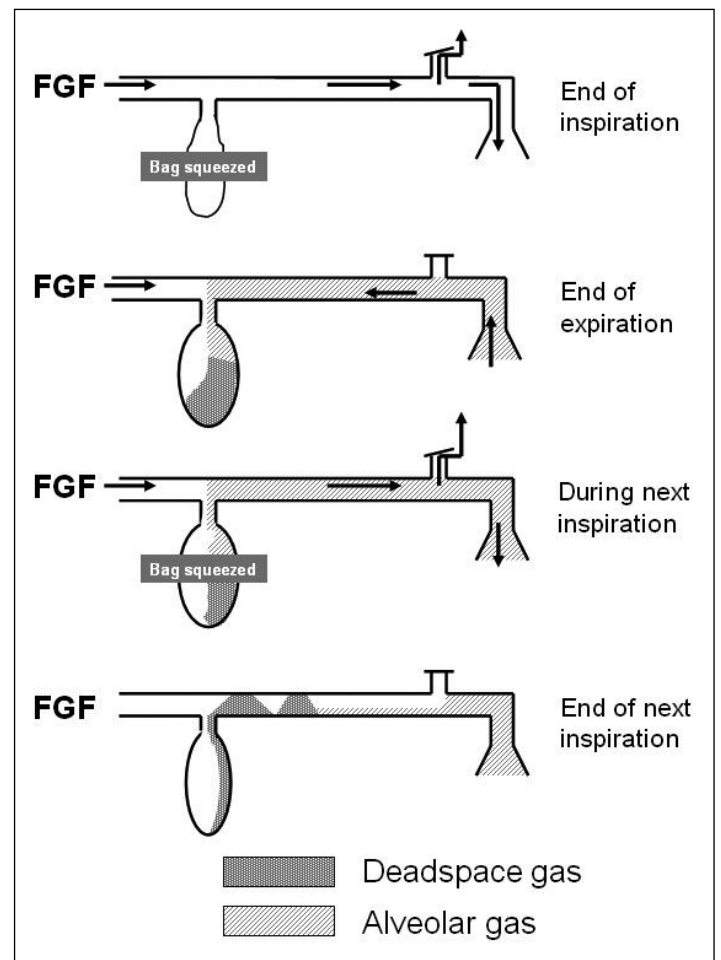


Figure 3. Mapleson A system with controlled or assisted ventilation

12-15l.min⁻¹) which is clearly very inefficient. In practice the Magill circuit should not be used for positive pressure ventilation except for short periods of a few minutes at a time.

Modifications of the Mapleson A system

A simple modification of the Mapleson A circuit is required to make it more efficient for controlled ventilation. This is achieved by substituting a non-rebreathing valve (such as an Ambu E valve) for the Heidbrink valve at the patient end of the circuit. Not only does this arrangement prevent rebreathing, but during manual ventilation the delivered minute volume will be the same as the desired FGF, which should be set at the rotameters. It is, however, a dangerous arrangement for spontaneous respiration because the valve may jam if the fresh gas flow is greater than the patient's minute volume.

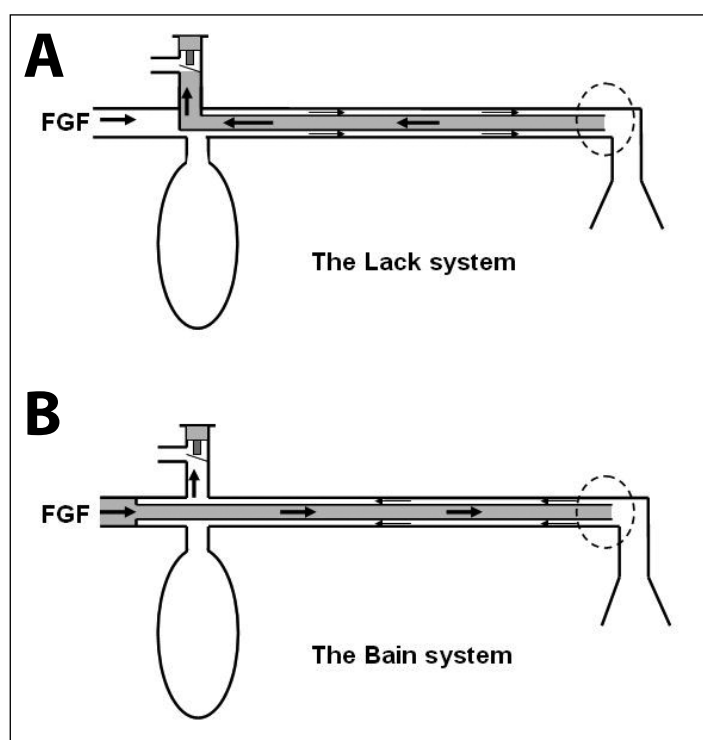


Figure 4. Coaxial anaesthetic breathing systems - the Bain (Mapleson D) and Lack (Mapleson A) systems. The coaxial tubing (shaded) avoids the need for fresh gas tubing (Bain) or an APL valve in the circuit near the patient. In the Bain system the coaxial tubing delivers fresh gas to a point in the system near the patient (dashed circle). In the Lack system it delivers expired gas to the APL valve

The Lack circuit

A disadvantage of the Magill system is that the expiratory valve is attached close to the patient making it awkward to use (particularly when a scavenging circuit is added). The Lack circuit (Figure 4A) is a Mapleson A system in which the exhaled gases travel down a central tube located within an outer corrugated tube towards the expiratory valve (co-axial system).

The inner tubing is wide enough to prevent an increase in the work of breathing and the expiratory valve is placed next to the reservoir bag, by the common gas outlet. The fresh gas flows required for both spontaneous and controlled ventilation are as described for the standard Mapleson A system.

Mapleson B and C breathing systems (Figure 1)

These systems are similar in construction, with the fresh gas flow entry and the expiratory valves located at the patient end of the circuit. They are not commonly used in anaesthetic practice, although the C system is commonly used on intensive care units (the Waters circuit), where it is used for IPPV or augmenting patient's spontaneous breaths during intubation and extubation. High flows of gases are needed to prevent rebreathing of CO₂ and this system was at one time combined with a canister of soda lime to absorb CO₂ (Waters' "to and fro" circuit). However the cannister proved too bulky for practical use and there was a risk of the patient inhaling soda lime dust.

Mapleson D breathing system

The Mapleson D, E and F systems are all functionally similar (Figure 1). They act as T-pieces with the FGF delivered to the patient end of the circuit and differ only in the presence of valves or breathing bags at the expiratory end of the circuit. These systems are all inefficient for spontaneous respiration (Figure 5). During expiration exhaled gas and fresh gas mix in the corrugated tubing and travel towards the reservoir bag. When the bag is full the pressure in the system rises and the expiratory valve opens venting to the atmosphere a mixture of fresh and exhaled gas. During the expiratory pause fresh gas continues to push exhaled alveolar gas down the tubing towards the valve. However, unless the FGF is at least twice the patient's minute volume, rebreathing of alveolar gas occurs. A FGF of at least 8-10l.min⁻¹ (150ml.kg⁻¹.min⁻¹) is required to prevent rebreathing in an adult.

When used for controlled ventilation the Mapleson D system functions more efficiently. During expiration the corrugated tubing and reservoir bag fill with a mixture of fresh and exhaled gas. Fresh gas fills the distal part of the corrugated tube during the expiratory pause prior to inspiration. When the bag is compressed this fresh gas enters the lungs and when the expiratory valve opens a mixture of fresh and exhaled gas is vented. The degree of rebreathing that occurs depends on the FGF. A FGF of 70ml.kg⁻¹.min⁻¹ is usually adequate for controlled ventilation; 100ml.kg⁻¹.min⁻¹ will result in a degree of hypocapnia (lowered CO₂ level in the blood).

Modifications of the Mapleson D system

The Bain co-axial circuit (Figure 4) is the most commonly used form of the Mapleson D system. Unlike the Lack co-axial circuit described above, fresh gas flows down the central narrow bore tubing (7mm internal diameter) to the patient and exhaled gases travel in the outer corrugated tubing (22mm internal diameter). The reservoir bag may be removed and replaced by a ventilator such as the Nuffield Penlon 200 for mechanical ventilation. Before use the Bain circuit should be carefully checked by the anaesthetist. The outer tubing of a Bain circuit is made of clear plastic and the inner green or black. If a leak develops in the inner tubing or it becomes detached from the fresh gas port, a huge increase in apparatus dead space occurs. In order to check for this, the lumen of the inner tubing should be occluded with a finger or the plunger of a 2ml syringe, demonstrating a rise in gas pressure within the anaesthetic circuit.

The degree of rebreathing that occurs during IPPV will depend on the FGF. In an adult, fresh gas flows of 70-80ml.kg⁻¹.min⁻¹ (6-7l.min⁻¹) will maintain a normal arterial carbon dioxide tension (normocapnia) and a flow of 100ml.kg⁻¹.min⁻¹ will result in mild hypocapnia.

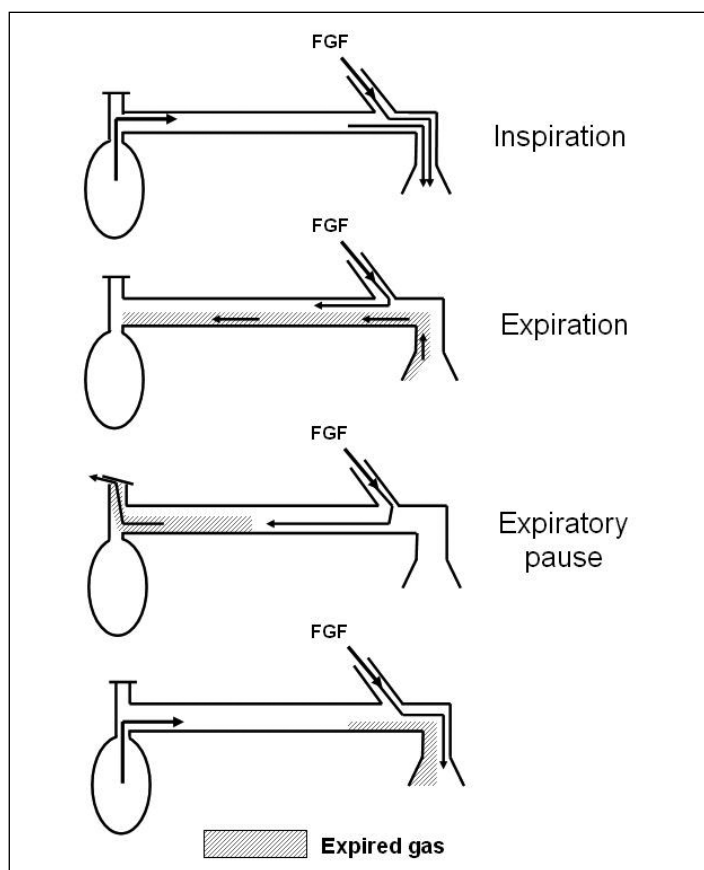


Figure 5. Mode of action of the Mapleson D breathing system during spontaneous ventilation

Mapleson E system

The Mapleson E system performs in a similar way to the Mapleson D, but because there are no valves and there is very little resistance to breathing it has proved very suitable for use with children. It was originally introduced in 1937 by P Ayre and is known as the Ayre's T-piece. The version most commonly used is the Jackson-Rees modification which has an open bag attached to the expiratory limb (classified as a Mapleson F system although it was not included in the original description by Professor Mapleson).

Movement of the bag can be seen during spontaneous breathing, and the bag can be compressed to provide manual ventilation. As in the Bain circuit, the bag may be replaced by a mechanical ventilator designed for use with children, such as a Penlon 200 with a Newton valve. This system is suitable for children under 20kg. Fresh gas flows of 2-3 times the minute volume should be used to prevent rebreathing during spontaneous ventilation, with a minimum flow of 3 l.min^{-1} . For example, a 4-year-old child weighing 20kg has a normal minute volume of 3 l.min^{-1} and would require a FGF of $6-9\text{ l.min}^{-1}$. During controlled ventilation in children normocapnia can be maintained with a fresh gas flow of $1000\text{ ml} + 100\text{ ml.kg}^{-1}$ - the 4-year-old weighing 20kg would need a total FGF of around 3 l.min^{-1} .

The Humphrey ADE circuit

The Mapleson A circuit is inefficient for controlled ventilation, as is the Mapleson D circuit for spontaneous ventilation. David Humphrey designed a single circuit that can be changed from a Mapleson A

system to a Mapleson D by moving a lever on the metallic block, which connects the circuit to the fresh gas outlet on the anaesthetic machine. The reservoir bag is situated at the fresh gas inlet end of the circuit, and gas is conducted to and from the patient down the inspiratory and expiratory limbs of the circuit. Depending on the position of the control lever at the Humphrey block, gases either pass through the expiratory valve or the ventilator port. When the lever is 'up' the reservoir bag and the expiratory valve are used, creating a Mapleson A type circuit. When the lever is in the 'down' position the bag and valve are bypassed and the ventilator port is opened, creating a Mapleson D system for controlled ventilation. If no ventilator is attached and the port is left open the system will function like an Ayre's T piece (Mapleson E).

Like all pieces of equipment, it is essential that the anaesthetist fully understands the function of this circuit before using it. If the lever on the Humphrey block is moved from 'up' to 'down' while gases are flowing, the breathing bag will remain full of gas but manual ventilation of the patient's lungs by compressing the bag will be impossible and may resemble complete obstruction of the breathing circuit.

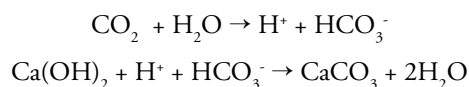


Figure 6. The Humphrey ADE circuit

CIRCLE SYSTEMS

An alternative to using high flow circuits is to absorb CO_2 from the expired gases which are then recirculated to the patient. These circuits, known as circle systems, were first used in 1926 and require smaller amounts of fresh gas each minute.

Carbon dioxide is removed from the expired gas by passage through soda lime, a mixture of 94% calcium hydroxide, 5% sodium hydroxide, and 1% potassium hydroxide which reacts with CO_2 to form calcium carbonate:



Soda lime also contains small amounts of silica to make the granules less likely to disintegrate into powder and a chemical dye which

changes colour with pH. As more carbon dioxide is absorbed the pH decreases and the colour of the dye changes from pink to yellow/white. When around 75% of the soda lime has changed colour it should be replaced. The soda lime canister should be mounted vertically on the anaesthetic machine to prevent the gases passing only through a part of the soda lime (streaming).

Fresh soda lime contains 35% water by weight which is necessary for the reaction between carbon dioxide and soda lime to take place. This generates considerable heat. The soda lime may rise in temperature to 40°C. This is an additional advantages of circle systems - the gases within the circle are warmed and humidified prior to inspiration. Baralyme is a commercially available CO₂ absorber which contains 5% barium hydroxide instead of sodium hydroxide.

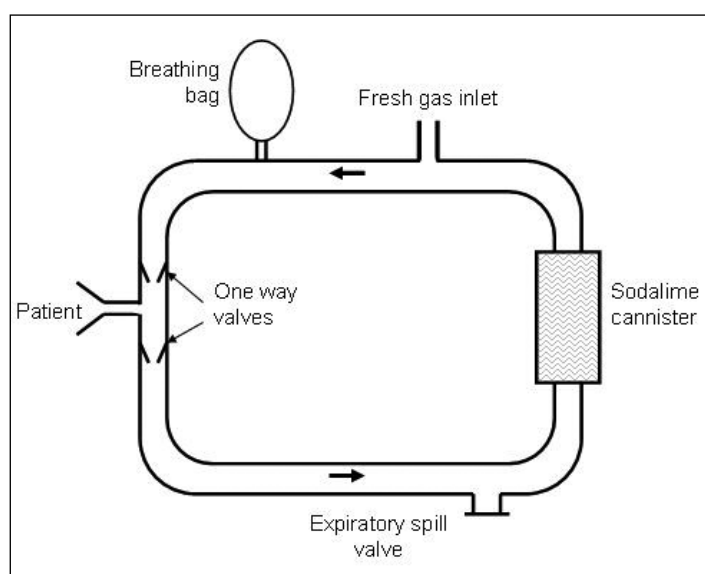


Figure 7. Schematic diagram showing the basic components of a circle breathing system

Design of circle systems

A circle system (Figure 7) is composed of two one-way valves (one on the inspiratory limb of the circuit from the patient and one on the expiratory limb), a reservoir bag, a fresh gas inlet, a canister of soda lime and an expiratory spill valve. Although there may be slight differences in the positioning of these components, all the systems function in the same way.

Vaporiser position

The vaporiser may be placed either outside the circle (VOC) on the anaesthetic machine in its conventional position, or rarely within the circle itself (VIC). Normal plenum vaporisers, with high internal resistance, cannot be used within the circle and a low internal resistance type vaporiser (such as the Goldman) is required. Drawover vaporisers such as the OMV are not recommended for use within the circle because of the risk of achieving dangerously high levels of inhalational agent. Since the gases are recirculated, if the vaporiser is placed in the circle, gas already containing volatile anaesthetic agent will re-enter the vaporiser and the resulting output will exceed the vaporiser setting. This is a particular danger during controlled ventilation. Vaporisers should only be placed inside the circle when inspired volatile anaesthetic

agent monitoring is available. It is safer to use conventional plenum vaporisers mounted on the anaesthetic machine outside the circle. In this case the maximum volatile anaesthetic agent concentration achievable within the circle cannot exceed that set on the vaporiser.

Practical use of circle systems - reducing the fresh gas flow

During the first five to ten minutes of anaesthesia using a volatile anaesthetic agent in oxygen and air, a large amount of the agent (and nitrous oxide, if used) is taken up by the patient, causing a reduction in the agent concentration within the system. In addition the total volume of the circle system (tubing and soda lime canister) is around 3 litres and this volume is also a reservoir of room air that needs to be replaced with anaesthetic agent and fresh gas. High fresh gas flows (roughly equivalent to the patient's minute volume) ensure that this wash-out of air from the system and the patient's functional residual capacity occurs rapidly. Wash-out of air from the patient's lungs is also dictated by the patient's minute volume. After 10 to 15 minutes, provided suitable agent monitoring is available, the fresh gas flow can be reduced to low flows.

Inspired anaesthetic gases should contain no carbon dioxide and a minimum of 30% oxygen. Exhaled alveolar gas contains a lower concentration of oxygen and around 5% carbon dioxide which is removed from the exhaled gas on passage through the soda lime. A small amount of fresh gas is added before the next breath. At low fresh gas flow rates (<1000ml.min⁻¹) the oxygen concentration within the circle is unpredictable, particularly when used with nitrous oxide, often dropping to 27%, or even to below 21%, at flows less than 0.5l.min⁻¹. Circle systems should preferably not be used at low flow rates without an oxygen analyser in the inspiratory limb. The lowest fresh gas flow rate of oxygen and nitrous oxide which can be used, whilst ensuring that the inspired oxygen concentration remains at a safe level, is 1500ml.min⁻¹ (nitrous oxide 900ml.min⁻¹ and oxygen 600ml.min⁻¹).

The margin of safety is far greater if only oxygen and a volatile agent is used in the circle system. Under these circumstances there is no risk of oxygen dilution and the flows may be reduced to 1000ml.min⁻¹. With flows of >1500ml.min⁻¹ the inspired concentration of volatile agent will be similar to that set on the vaporiser. With flows <1500ml.min⁻¹ the volatile agent concentration may fall within the circuit and the setting on the vaporiser may need to be increased. This occurs because vaporisers function less efficiently at low fresh gas flows, but also because recycled gas in the circle contains less agent (after some has been taken up by the patient), and so dilutes the agent joining the circle in the fresh gas.

Halothane, isoflurane and enflurane are all safe to use in circle systems with soda lime, however trichloroethylene (no longer used in the USA or UK) produces a toxic metabolite and must not be used. When the circle system is not in use all fresh gas flows should be turned off to avoid wastage and to prevent the soda lime from drying out.

Several paediatric circle systems have been developed using smaller bore tubing and a one litre reservoir bag. The work involved in breathing through these systems is no greater than with a conventional Mapleson F system.

CONCLUSION

There are many different continuous flow breathing systems available, and this review has concentrated on those that are most commonly used.

With patient safety in mind, it is essential that the anaesthetist

routinely checks the anaesthetic circuit before use.

It is important to have a thorough understanding of the function and pitfalls of a particular system, as well as the minimum fresh gas flows for each system, before using it.

SI UNITS

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The International System of Units was eventually defined in 1971 by the CGPM (Conférence Générale des Poids et Mesures) and is based on the metric system. It includes seven base quantities which are mutually independent:

Base quantity	Name	Symbol
length	metre	m
mass	kilogram	kg
time	second	s
electric current	ampere	A
thermodynamic temperature	kelvin	K
amount of substance	mole	mol
luminous intensity	candela	cd

Other quantities are derived quantities and can be defined by equations using the base units, for example:

Derived quantity	Name	Symbol
area	square metre	m ²
volume	cubic metre	m ³
speed, velocity	metre per second	m.s ⁻¹
acceleration	metre per second squared	m.s ⁻²
specific volume	cubic meter per kilogram	m m ³ .kg ⁻¹
current density	ampere per square meter	A.m ⁻²

There are 20 SI prefixes which form multiples of the SI units:

Factor	Name	Symbol	Factor	Name	Symbol
10 ²⁴	yotta	Y	10 ⁻¹	deci	d
10 ²¹	zetta	Z	10 ⁻²	centi	c
10 ¹⁸	exa	E	10 ⁻³	milli	m
10 ¹⁵	peta	P	10 ⁻⁶	micro	μ or mc
10 ¹²	tera	T	10 ⁻⁹	nano	n
10 ⁹	giga	G	10 ⁻¹²	pico	p
10 ⁶	mega	M	10 ⁻¹⁵	femto	f
10 ³	kilo	k	10 ⁻¹⁸	atto	a
10 ²	hecto	h	10 ⁻²¹	zepto	z
10 ¹	deka	da	10 ⁻²⁴	yocto	y

Humidification

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Summary

Humidity is an important aspect of delivering gases to patients in theatres and intensive care. Every anaesthetist is expected to understand the principles of humidification of gases. The consequences of not humidifying gases can be serious. This article will cover the basics of humidity and techniques of humidification of gases.

WHAT IS HUMIDITY?

Humidity is a measure of the amount of water vapour in a gas. Absolute humidity is defined as actual mass of water vapour present in a known volume of gas. The absolute humidity of air in the upper airway of humans is about 34g.m^{-3} and it reaches a peak of 43g.m^{-3} as it reaches the alveoli. Relative humidity is defined as the ratio of the mass of water vapour in a given volume of gas to the maximum amount of water vapour that the same gas can hold at the same temperature. Relative humidity is expressed as a percentage.

ROLE OF HUMIDIFICATION OF GAS

The air we breathe becomes fully saturated with water vapour as it passes through nose to finally reach the alveoli. This humidification maintains mucosal integrity, ciliary activity, prevents the drying of secretions and helps in easy expulsion of respiratory secretions when coughing. Lack of humidification (e.g. ventilating a patient with dry gas through a tracheal or tracheostomy tube) can result in cracking of mucosa, drying of secretions, keratinisation of the tracheo-bronchial tree, reduction in ciliary activity, atelectasis and infection. Over-humidification has its own complications. It can result in water intoxication, especially in neonates and infants in intensive care, water clogging and airway burns.¹ Various methods of measuring and providing humidification are described below. The ideal humidifier should be easy to use, efficient, have low resistance to flow of gas, and should be economical and safe. Humidification can be used with any breathing circuit and may be provided for air, oxygen and a mixture of gases including anaesthetic gases.

MEASUREMENT OF HUMIDITY

Humidity is measured using a hygrometer. The following instruments have been used to measure humidity.^{2,3} Most measure relative humidity.

Hair hygrometer

This is based on the principle that the length of the hair increases with increasing humidity. It is fairly accurate between 30 and 90%.

Wet and dry bulb hygrometer

Two mercury thermometers, one in ambient temperature and the other in contact with water through a wick are used. The difference in the temperature reading in these two thermometers is a measure of rate of evaporation of water, that in turn depends on humidity.

Regnault's hygrometer

Air is blown through a silver tube containing ether. At *dew point*, condensation occurs on the outer surface of the tube. Ambient air is fully saturated at this temperature. The ratio of saturated vapour pressure (SVP) at *dew point* to SVP at ambient temperature gives relative humidity. This technique is more accurate than the first two.

Mass spectrometer

This instrument uses the principle of reduction in the ultraviolet light transmitted through the medium containing water vapour.²

METHODS OF HUMIDIFICATION

Heat and moisture exchanger (HME) filter

HME filters contain materials such as ceramic fibre, paper, cellulose, fine steel or aluminium fibres in a hygroscopic medium such as calcium chloride or silica gel (Figure 1). Warm, humidified, expired gas passes through the HME, water vapour condenses within the medium and is then re-used for humidification of the inspired gas. The HME is warmed by the latent heat of water condensing on it. This heat is also released during subsequent inspiration. Some filters have bacterial (and/or viral) filtering properties with efficiencies more than 99.9977%.⁴ The microbial filtering property may be due to:

Direct interception

If the particle is more than 1mcm (micrometer), it is physically prevented from passing through the pores.⁵

Inertial impaction

Smaller particles ($<0.5\text{mcm}$) are held by the filtering medium by van der Waals electrostatic forces.⁵

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Diffusional interception

Particles less than 0.5mcm move freely and randomly (Brownian movement) and subsequently swell up and get filtered by the pores.⁵

Electrostatic attraction

Charged particles are attracted by oppositely charged fibres.⁵



Figure 1. Heat and moisture exchanger (HME)

The main advantages of HME filters are:

- Easy to use in breathing circuits.
- Cheap and disposable.
- 60-70% relative humidity achieved.
- Temperature achieved ranges from 29-34°C.
- Can be incorporated as a microbial filter.

The main disadvantages of HME filters are:

- Need replacing every 24 hours (maximum).
- Secretions can block the filter.
- Resistance to flow of gas can be up to 2cmH₂O.
- Can add to the weight of the circuit – may be significant in neonates/infants.
- Increase circuit dead space.

Water bath humidifier

A simple **cold water bath humidifier** allows gas to flow through water and carries water vapour as it bubbles out. This type is less efficient as bubbles are large and the loss of heat from the latent heat of vaporization reduces humidity. The vapour output can be increased by warming the water using electricity (**hot water bath humidifier**) but must incorporate a thermostat to maintain an operating temperature at about 40°C (Figure 2). At 37°C, near full saturation can be achieved. A water trap is placed between the humidifier and the patient and is placed below the level of the patient. In a typical hot water bath humidifier, gas flows over the water to become saturated with water vapour. In the **cascade humidifier**, gas bubbles through perforations at the bottom of the water reservoir. Vapour output depends on temperature of the water, gas flow and surface area of contact.³

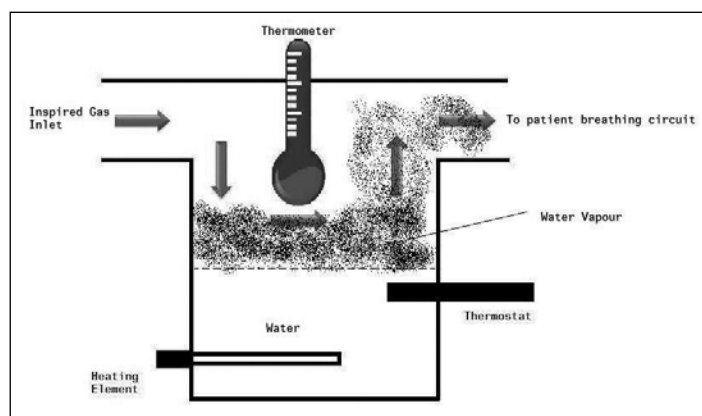


Figure 2. Hot water bath humidifier

The main problems of hot water humidifier are:

- Water spillage into the breathing circuit and even into tracheo-bronchial tree. A water trap will help reduce this problem.
- Airway burns due to thermostat failure and overheating.
- Colonization of water with harmful bacteria can occur. This may be reduced by heating the water to 60°C.

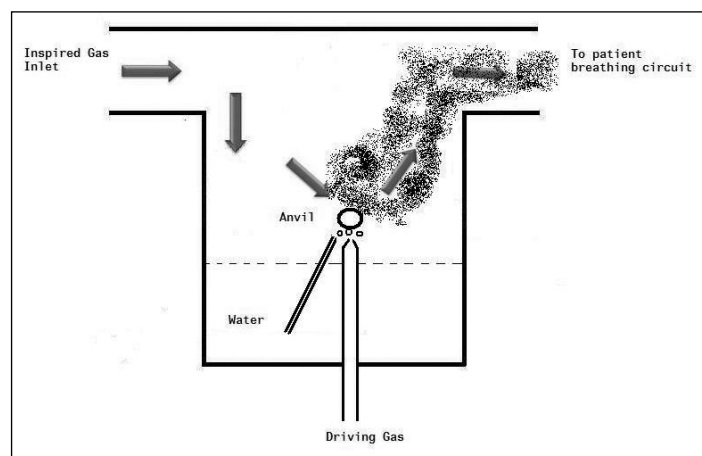


Figure 3. A nebuliser

Nebulisers

Nebulisers produce water vapour in the form of microdroplets (1-20mcm). There are three types of nebulisers. In a **gas driven nebuliser** (Figure 3), gas is passed through a narrow orifice that produces a pressure gradient. This results in water being drawn up through the tube and broken into a fine spray as it comes in contact with the high-speed gas jet. Even smaller droplets can be produced if this spray of gas hits an anvil or a baffle. Most of the droplets are in the range of 2-4mcm and deposit in the upper airway with a very small amount reaching the smaller bronchioles. In a **spinning disc nebuliser**, the rotating disc produces microdroplets when water is drawn onto the disc. The **ultrasonic nebuliser** has a transducer head immersed in water vibrating at ultrasonic frequency (3MHz). Ultrasonic nebulizers produce microdroplets less than 2mcm which are capable of reaching alveoli and are therefore a very efficient form of humidification.⁵

A comparison of the various humidifiers is given in Table 1.

Table 1. Comparison of various humidifiers (fully saturated gas at 37 °C has an absolute humidity of 44g.m⁻³)

Type of humidifier	Absolute humidity produced (approximate) g.m ⁻³
Cold water bath	10
Heat and moisture exchanger	25
Hot water bath	40
Gas driven nebuliser	60
Ultrasonic nebuliser	90

ACKNOWLEDGEMENT

I am grateful to Mr. Aravinda A Hegde, Bangalore, India for his help in designing the figures in this article.

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Anaesthetic Gas Scavenging

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THE IMPORTANCE OF SCAVENGING IN THEATRE

Possible adverse health effects are an increased risk of spontaneous abortion in females, the increased likelihood of male anaesthetists to father daughters, decreased fertility, a potential increase in haematological malignancy, renal and liver dysfunction and decreased mental performance. One explanation for these effects is inhibition of methionine synthase by nitrous oxide, causing impairment of deoxyribonucleic acid (DNA) synthesis. However the evidence for these effects is not robust, with studies giving conflicting results.

The removal of waste gases is therefore an issue of health and safety and a legal requirement. Strict regulations are overseen by bodies such as the Control of Substances Hazardous to Health (COSHH) in the UK and the National Institute for Occupational Safety and Health (NIOSH) in the USA.

The maximum acceptable levels are usually given as an 8 hour time weighted average (TWA) and are listed in Table 1. Sevoflurane and desflurane have yet to be given limits but 50 ppm (parts per million) is recommended based on their similarity to enflurane.

SCAVENGING SYSTEMS

The scavenging system must be able to collect waste gases from the exhaust port of the anaesthetic circuit or ventilator, transfer them to a receiving system and from there dispose of them outside the working environment. Systems generally have four components which can vary in design and function (Figure 1). On modern anaesthetic machines they are designed for use with a central suction system, but the four components can equally be fabricated from basic materials for use in the resource poor situation.

Collecting system

This gathers excess waste gases from either the APL (adjustable pressure limiting) valve of a breathing circuit or from the exhaust port of a ventilator. To avoid accidental misconnection, the outlet fitting should be different to the 22mm and 15mm conical connections of standard breathing systems. The collecting system is usually a shrouded APL valve for use with Mapleson circuits A-D (Figure 2). One way valves can also be scavenged with either commercially available systems or, from personal experience, can easily be manufactured to fit over the expiratory port. The collecting system must not cause resistance to expiration and, for this reason, it is difficult

to scavenge T-piece systems for use with paediatric patients. A totally open system has previously been described, in which the expired gases are directed and entrained toward a scavenging dish with high flow suction. Alternatively the scavenging device shown in Figure 3 is available.

Transfer system

This usually consists of a length of tubing with a connector at either end. These

Summary

The use of anaesthetic gases, such as nitrous oxide and volatile agents, within the closed environment of the operating theatre may lead to the chronic exposure of staff with potential adverse consequences on health.

Certain agents, notably ether are potentially flammable and should not be allowed to accumulate.

This article describes the component features of anaesthetic gas scavenging systems.

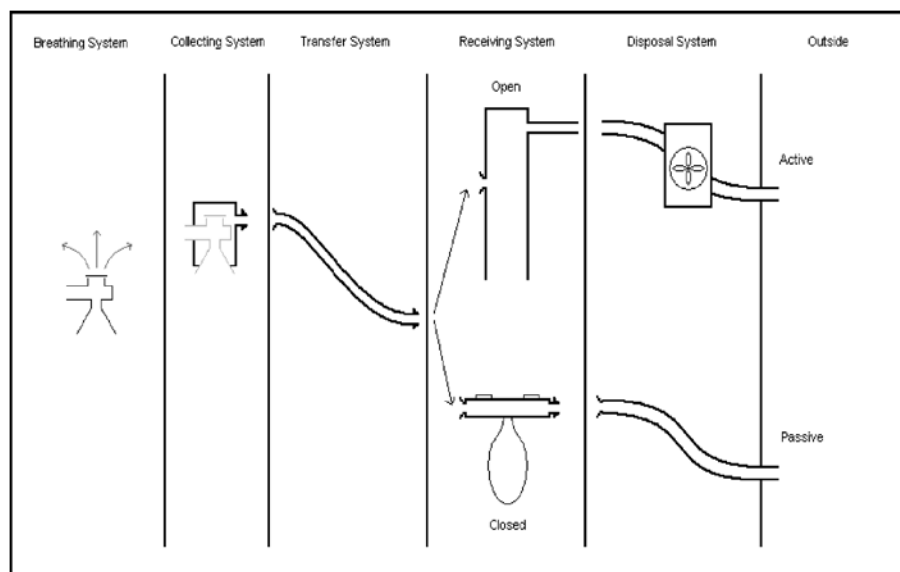


Figure 1. Components of a scavenging system showing the four components; collecting, transfer, receiving and disposal

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Table 1. Proscribed maximum levels for anaesthetic gases (TWA = time weighted average, ppm = parts per million)

Substance	Permitted Maxima in ppm as 8 hour TWA	
	UK	USA
N ₂ O	100	25
Isoflurane	50	2
Enflurane	50	2
Halothane	10	2

should also be of a different gauge to the breathing system to avoid accidental misconnection. The tubing should be less than a metre long to avoid the risk of kinking.

Receiving system

This is the main interface between the breathing system and the disposal system and must protect the patient from excessive positive or negative pressures. It also provides reservoir capacity to help cope with the peak expiratory flows from the patient circuit.

Receiving systems can be either open or closed. In a closed system, the reservoir is usually a distensible bag with positive and negative pressure release valves. This system is still popular in veterinary anaesthesia, but is much less common in developed world hospitals. In an open system, the reservoir is often a tubular structure open to the atmosphere, thus providing an air-break between the disposal system and the breathing system (Figure 4). The open system relies on an active disposal system to function.

Disposal system

These can be active or passive. In passive systems (driven by the patient's expiratory effort), exhaust gases pass along a tube through



Figure 2. The collecting system of a Bain circuit is a shroud (A) around the adjustable pressure limiting (APL) valve (B). The transfer system is labelled C



Figure 3. A scavenging device for the Ayres T-piece. Note that the reservoir bag has a closed end



Figure 4. An open receiving system; A - transfer system from breathing circuit; B - connection to wall suction

an outside wall or window and are discharged to the atmosphere. Tubing should be as short and wide as possible to minimise resistance. The outlet should be protected from the elements and should be covered with a mesh to prevent the ingress of insects. Care should be taken not to position the exterior tube in a windy position as high winds can create suction which could be transmitted to the patient. It is also possible to route a passive system via the air circulation system (if one exists), provided that it is not a recirculation system. Charcoal canisters are another passive device and are very portable. They act by absorbing halogenated gases but do not render them inert. If heated, the charcoal releases the gases. This method will not filter nitrous oxide and

they need to be refilled after every 12 hours of use, which can be a messy undertaking.

In active systems a fan or pump in the disposal system draws the anaesthetic gases through. Active methods are most effectively and safely used with open receiving systems and are the most common form of scavenging in the developed world, with hospitals now built with dedicated central vacuum systems. Fans can only function at low pressure and therefore should incorporate wide bore tubing, whereas pump systems can develop high pressures and can be used with narrow tubing. With all active systems it is mandatory to have a mechanism to protect the patient against negative pressures.

OTHER METHODS OF MINIMISING THEATRE POLLUTION

Other methods of minimising theatre pollution and reducing the impact of leaking scavenging systems, filling of vaporisers, bag-valve-mask draw-over anaesthesia, and patients in recovery areas (where expired gases are not scavenged) include adequate ventilation of theatres with 15 air changes per hour, if possible. Circle breathing systems utilising low flows will also help to reduce production of waste gases. Utilising total intravenous anaesthesia and loco-regional anaesthesia avoid the risks altogether.

Practical Applications of Pulse Oximetry

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INTRODUCTION

Pulse oximeters are now a standard part of perioperative monitoring which give the anaesthetist an indication of the patient's cardiorespiratory status. Following successful use during anaesthesia, in the intensive care unit and in the recovery room, oximetry has been increasingly introduced in other areas of the hospital such as general wards, high-dependency areas within wards and sites of interventional procedures (radiology and endoscopy units). Pulse oximeters have pitfalls and limitations and staff training is essential to avoid inadvertent misuse and potential patient harm. This article aims to give an overview of the function and use of pulse oximetry that is appropriate to both regular and occasional users.

Pulse oximeters measure the oxygen saturation of haemoglobin (Hb) in arterial blood, using a probe attached to the patient's finger or ear lobe that is linked to a microprocessor unit. The unit displays the percentage of haemoglobin saturated with oxygen, together with an audible signal for each pulse beat, a calculated heart rate and in some models, a graphical display of the blood flow past the probe. Audible alarms which can be programmed by the user are provided. An oximeter detects hypoxia before the patient becomes clinically cyanosed.

Two basic physical principles form the basis of oximetry:

- First, the absorption of light at two different wavelengths (660 and 940nm) by haemoglobin differs depending on the proportion of haemoglobin molecules that are bound to oxygen ('oxygenated'). By calculating the absorption at the two wavelengths, the processor can compute the proportion of haemoglobin that is oxygenated.
- Second, the light signal following transmission through the tissues has a pulsatile component, resulting from the changing volume of arterial blood with each pulse beat. This can be distinguished by the processor from the non-pulsatile component resulting from venous, capillary and tissue light absorption.

The function of a pulse oximeter is affected by many variables, including:

- ambient light,
- shivering,
- abnormal haemoglobins,
- pulse rate and rhythm,
- vasoconstriction,
- cardiac function.

A pulse oximeter gives no indication of a patient's ventilation, only of their oxygenation, and extreme hypercapnoea may be overlooked if supplemental oxygen is being given. In addition, there may be a delay between the occurrence of a potentially hypoxic event, such as respiratory obstruction, and a pulse oximeter detecting low oxygen saturation. However, oximetry is a useful non-invasive monitor of a patient's cardiorespiratory system, which has undoubtedly improved patient safety in many circumstances.

WHAT DOES A PULSE OXIMETER MEASURE?

The oxygen saturation of haemoglobin in arterial blood

This is a measure of the average amount of oxygen bound to each haemoglobin molecule. The percentage saturation is given as a digital readout together with an audible signal, varying in pitch depending on the oxygen saturation.

The pulse rate

This is given as beats per minute, averaged over 5 to 20 seconds (this period can be varied on some monitors).

In addition, systolic blood pressure can be estimated by noting the pressure at which the oximetry trace reappears during deflation of a proximal non-invasive blood pressure cuff.

WHAT DOESN'T A PULSE OXIMETER MEASURE?

- The **oxygen content** of the blood,

Summary

Pulse oximetry is a simple non-invasive method of monitoring patients which can be used in a wide variety of circumstances, and in the face of limited resources. The pulse oximeter represents a wise choice of monitor since, with appropriate training, it allows assessment of several different patient parameters.

The basic science principles, pitfalls and clinical use of pulse oximeters are discussed.

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- The amount of **oxygen dissolved** in the blood,
- The respiratory rate or tidal volume i.e. **ventilation** (and therefore carbon dioxide clearance),
- The **cardiac output or blood pressure**, although information about blood flow to the peripheries can be inferred.

PRINCIPLES OF MODERN PULSE OXIMETRY

Oxygen is carried in the bloodstream, mainly bound to haemoglobin. One molecule of haemoglobin can carry up to four molecules of oxygen, which is then 100% saturated with oxygen. The average percentage saturation of a population of haemoglobin molecules in a blood sample is the oxygen saturation of the blood. In addition, a very small quantity of oxygen is carried dissolved in the blood, which can become important if the haemoglobin level is extremely low. The latter, however, is not measured by pulse oximetry.

The relationship between the arterial partial pressure of oxygen (PaO_2) and the oxygen saturation is described by the haemoglobin-oxygen dissociation curve (see Figure 1). The sigmoid shape of this curve represents the fact that unloading of oxygen is facilitated in the peripheral tissues, where the PaO_2 is low and oxygen is required for cellular respiration. The curve may be shifted to the left or right by various patient characteristics, such as pH, temperature and recent blood transfusion.

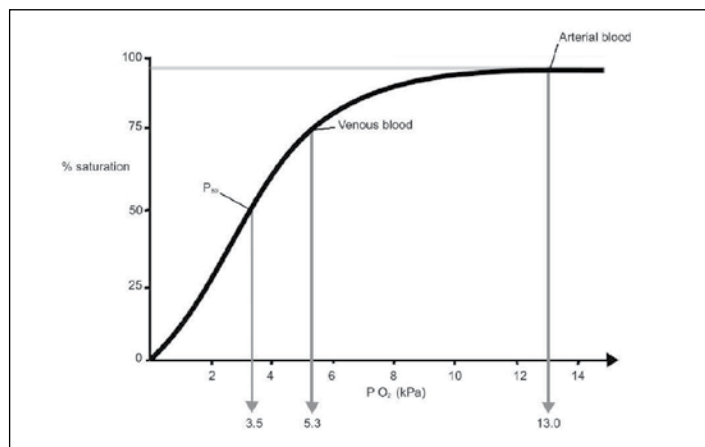


Figure 1. The haemoglobin-oxygen dissociation curve

A pulse oximeter consists of a peripheral probe, together with a microprocessor unit, displaying a waveform, the oxygen saturation and the pulse rate. Most oximeters also have an audible pulse tone, the pitch of which is proportional to the oxygen saturation - useful when one cannot see the oximeter display. The probe is placed on a peripheral part of the body such as a digit, ear lobe or the nose. Within the probe are two light-emitting diodes (LEDs), one in the visible red spectrum (660nm) and the other in the infrared spectrum (940nm). The beams of light pass through the tissues to a photodetector. During passage through the tissues, some light is absorbed by blood and soft tissues, depending on the concentration of haemoglobin. The amount of light absorption at each light frequency depends on the degree of oxygenation of haemoglobin within the tissues (see Figure 2). Note that an *isosbestic* point describes a wavelength at which absorption of light by a substance remains constant as the equilibrium between its component substances is shifted.

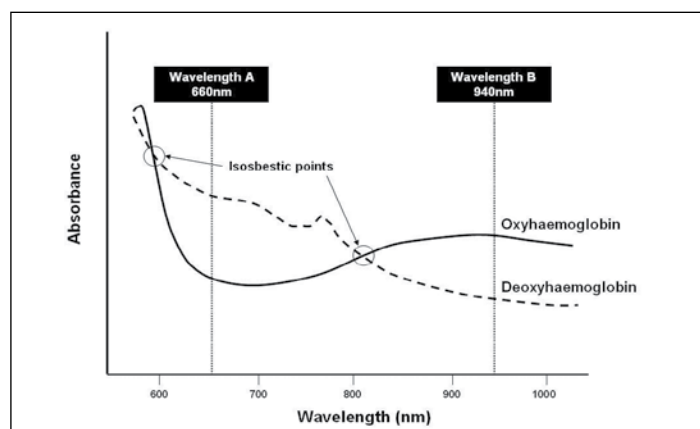


Figure 2. The spectrum of absorbances for haemoglobin and oxyhaemoglobin, showing the isosbestic points

The microprocessor can select out the absorbance of the pulsatile fraction of blood, i.e. that due to arterial blood, from constant absorbance due to non-pulsatile venous or capillary blood and other tissue pigments. Several recent advances in microprocessor technology have reduced the effects of interference on pulse oximeter function. Time division multiplexing, whereby the LED's are cycled: red on, then infrared on, then both off, many times per second, helps to eliminate background 'noise'. Quadrature division multiplexing is a further advance in which the red and infrared signals are separated in phase rather than time and then recombined in phase later. In this way, an artefact due to motion or electromagnetic interference may be eliminated since it will not be in the same phase of the two LED signals once they are recombined.

Saturation values are averaged out over 5 to 20 seconds. The pulse rate is also calculated from the number of LED cycles between successive pulsatile signals and averaged out over a similar variable period of time, depending on the particular monitor.

From the proportions of light absorbed at each light frequency, the microprocessor calculates the ratio of the two. Within the oximeter memory is a series of oxygen saturation values obtained from experiments performed on human volunteers, given increasingly hypoxic mixtures of gases to breathe. The microprocessor compares the ratio of absorption at the two light wavelengths measured with these stored values, and then displays the oxygen saturation digitally as a percentage and audibly as a tone of varying pitch. As it is unethical to desaturate human volunteers below 70%, it is vital to appreciate that oxygen saturation values below 70% obtained by pulse oximetry are unreliable.

Reflection pulse oximetry uses reflected rather than transmitted light on a single-sided monitor. It can therefore be used more proximally anatomically e.g. forehead, bowel, although it may be difficult to secure. Other than using specific reflection spectra, the principles are the same as for transmission oximetry.

PRACTICAL TIPS TO THE SUCCESSFUL USE OF PULSE OXIMETRY

- Plug the pulse oximeter in to an electrical socket, if available, to recharge the batteries.

- Turn the pulse oximeter on and wait for it to go through its calibration and check tests.
- Select the probe you require with particular attention to correct sizing and where it is going to go. The digit should be clean (remove nail varnish).
- Position the probe on the chosen digit, avoiding excess force.
- Allow several seconds for the pulse oximeter to detect the pulse and calculate the oxygen saturation. Resist the temptation to impatiently move the probe from finger to finger without waiting for the reading to register.
- Look for a displayed waveform. Without this, any reading is meaningless.
- Read off the displayed oxygen saturation and pulse rate.
- If in doubt, rely on your clinical judgement, rather than the value the machine gives.

Be cautious interpreting figures where there has been an instantaneous change in saturation - for example 99% falling suddenly to 85%. This is not physiologically possible.

Alarms

- Prior to each case check that the alarms are set at an appropriate level.
- If the 'Low Oxygen Saturation' alarm sounds, check the positioning of the probe and that there is a good pulse waveform. Look to see if the patient is clinically cyanosed and check that the patient is conscious if that is appropriate. Check the airway and make sure the patient is breathing adequately. Lift the chin or apply other airway manoeuvres as appropriate. Give oxygen if necessary. Call for help.
- If the 'Pulse Not Detected' alarm sounds, look for the displayed waveform on the pulse oximeter. Feel for a central pulse. If there is no pulse, call for help and start the procedures for Basic and Advanced Life Support. If there is a pulse, try repositioning the probe, or put the probe on a different digit.
- On most pulse oximeters, the alarm limits for oxygen saturation and pulse rate can be altered according to your needs. However, do not alter an alarm just to stop it sounding - it could be telling you something important!

USES OF PULSE OXIMETRY

- A simple, portable 'all-in-one' monitor of oxygenation, pulse rate and rhythm, suitable for use in all settings.
- As a safe, non-invasive monitor of the cardiorespiratory status of high-dependency patients - in the emergency department, during general and regional anaesthesia, postoperatively and in the intensive care unit. This includes procedures such as endoscopy, where drugs such as midazolam are frequently given to more elderly patients. Pulse oximeters detect the presence of cyanosis more reliably than even the experienced doctors using their clinical judgement.
- During the transport of patients, especially when noise is an issue,

for example in aircraft, helicopters or ambulances. The audible tone and alarms may not be heard, but if a waveform can be seen, together with an acceptable oxygen saturation, this gives a global indication of a patient's cardiorespiratory status.

- To assess the viability of limbs after plastic and orthopaedic surgery and, for example, following vascular grafting, or where there is soft tissue swelling. As a pulse oximeter requires a pulsatile signal under the sensor, it can detect whether a limb is getting a blood supply.
- As a means of reducing the frequency of blood gas analysis in intensive care patients, particularly in paediatric practice where vascular (arterial) access may be more difficult.
- To limit oxygen toxicity in premature neonates supplemental oxygen can be tapered to maintain an oxygen saturation of 90% - thus avoiding the damage to the lungs and retinas of neonates. Although pulse oximeters are calibrated for adult haemoglobin, HbA, the absorption spectra of HbA and HbF are almost identical over the range used in pulse oximetry, so the technique remains reliable in neonates.
- During thoracic anaesthesia, and particularly one-lung anaesthesia, to determine whether oxygenation via the remaining lung is adequate or whether increased concentrations of oxygen must be given.
- Fetal oximetry - a developing technique that uses reflectance oximetry, using LEDs of 735nm and 900nm. The probe is placed over the temple or cheek of the fetus, and needs to be sterile and sterilisable. They are difficult to secure and the readings are variable, for physiological and technical reasons. Hence the trend is more useful than the absolute value.

LIMITATIONS OF PULSE OXIMETRY

- Oximetry is **not a monitor of ventilation**. Carbon dioxide levels will rise where a patient's minute volume is low. When supplementary oxygen is given, the oxygen saturations may remain normal as hypercarbia causes decreased conscious level, respiratory acidosis with the risk of cardiorespiratory collapse. Knowledge of this pitfall is essential for safe use of pulse oximetry.
- Pulse oximetry may be less effective in **critically ill or injured patients**. Tissue perfusion may be poor (due to hypovolaemia, severe hypotension, cold, cardiac failure, some cardiac arrhythmias or peripheral vascular disease) and thus the oximeter probe may not detect a pulsatile signal. More central sites for probe positioning include the nose, and the lips, although placement at these sites for prolonged periods may cause pressure necrosis. Application of a paediatric probe to an oropharyngeal airway has been shown in case reports to provide effective oximetry (Figure 3).¹
- **Waveform presence**. If there is no waveform visible on a pulse oximeter, any percentage saturation values obtained are meaningless.

In the following situations the pulse oximeter readings may not be accurate.



Figure 3. Pharyngeal pulse oximetry may be achieved in shocked patients using a paediatric pulse oximetry probe taped to an oropharyngeal (Guedel) airway¹

- **Venous congestion**, particularly when caused by tricuspid regurgitation, may produce venous pulsations which may produce low readings with ear probes. Venous congestion of the limb may affect readings as can a poorly positioned probe. When readings are lower than expected, it is worth repositioning the probe. In general, however, if the waveform on the flow trace is good, then the reading will be accurate.
- **Bright overhead lights** in theatre may cause the oximeter to be inaccurate, and the signal may be interrupted by surgical diathermy. **Shivering** may cause difficulties in picking up an adequate signal.
- Pulse oximetry cannot distinguish between different forms of haemoglobin. **Carboxyhaemoglobin** (haemoglobin combined with carbon monoxide) is registered between 90 to 100% oxygenated haemoglobin and 10% desaturated haemoglobin - therefore the oximeter will overestimate the saturation. A technique called CO-oximetry (see below) is the only available method of estimating the severity of carbon monoxide poisoning.
- The presence of **methaemoglobin** (rarely caused by prilocaine overdose) prevents the oximeter working accurately and the readings will tend towards 85%, regardless of the true saturation.
- Methylene blue may be used in surgery to highlight the parathyroids, to guide dissection of the sentinel axillary lymph node in surgery for breast cancer or to treat methaemoglobinaemia. Methylene blue causes a shortlived reduction in saturation.
- Nail varnish may cause falsely low readings.

Pulse oximetry is not affected by jaundice, dark skin or anaemia.

- **'Lag monitor'** - the partial pressure of oxygen may have fallen a great deal before the oxygen saturation starts to fall. If a healthy adult patient is given 100% oxygen to breathe for a few minutes and then ventilation ceases for any reason, several minutes may elapse before the oxygen saturation starts to fall. There is also a **response delay** due to signal averaging. This means that there is

a delay after the actual oxygen saturation starts to drop because the signal is averaged out over 5 to 20 seconds.

- **Patient safety** - there are reports of skin burns or pressure damage under the probe because some early probes had a heater unit to ensure adequate skin perfusion. The probe should be correctly sized, and should not exert excessive pressure. Special probes are now available for paediatric use.
- The **penumbra effect** re-emphasises the importance of correct probe positioning. This effect causes falsely low readings and occurs when the probe is not symmetrically placed, such that the pathlength between the two LEDs and the photodetector is unequal, causing one wavelength to be 'overloaded'. Repositioning of the probe often leads to sudden improvement in saturation readings. The penumbra effect may be compounded by the presence of variable blood flow through cutaneous pulsatile venules. Note that the waveform may appear normal despite the penumbra effect, as it measures predominantly one wavelength only.

ALTERNATIVES TO PULSE OXIMETRY

Bench CO-oximetry

This is the gold standard and is the classic method by which a pulse oximeter is calibrated. The CO-oximeter calculates the actual concentrations of haemoglobin, deoxyhaemoglobin, carboxyhaemoglobin and methaemoglobin in the sample and hence calculates the actual oxygen saturation. CO-oximeters are much more accurate than pulse oximeters - to within 1%, but they give a 'snapshot' of oxygen saturation, are bulky, expensive and require constant maintenance, as well as requiring a sample of arterial blood to be taken.

Blood gas analysis

This requires an invasive sample of arterial blood. It gives the 'full picture', including arterial partial pressure of oxygen and carbon dioxide, arterial pH, actual and standardised base excess and actual and standardised bicarbonate concentrations. Many blood gas analysers report a calculated saturation which is less accurate than that provided by the pulse oximeter.

SUMMARY

Pulse oximeters give a useful non-invasive estimation of the arterial haemoglobin oxygen saturation. They are useful in anaesthesia, recovery, intensive care (including neonatal) and patient transport, providing an adjunct to clinical assessment of a patient. It is important to recognise and remember that pulse oximeters give no direct indication of a patient's ventilation, only of their oxygenation and that there is a time-lag in detection of a hypoxic event. Sources of inaccuracy include ambient light, shivering, vasoconstriction, shock and the presence of abnormal haemoglobins.

FURTHER READING

1. Yu H, Liu B. Successful use of pharyngeal pulse oximetry with the oropharyngeal airway in severely shocked patients. *Anaesthesia* 2007; **62**: 734-6

Pressure and Blood Pressure Measurement

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FORCE AND PRESSURE

Force causes an object to move in a certain direction. The SI (Système International d'Unités) of force is the newton, one newton (N) being the force which, when applied to a mass of 1kg, will give the mass an acceleration of 1 metre per second squared (m.s^{-2}).

Pressure is defined as force per unit area. The SI unit of pressure is the pascal, one pascal (Pa) being equal to 1 newton, distributed over an area of 1m^2 (1N.m^{-2}). One newton is a small force and one m^2 is a relatively large area, so a pascal is a small amount of pressure. Pressure is therefore commonly expressed in kilopascals (kPa).

$$\text{Pressure} = \frac{\text{Force}}{\text{Area}}$$

This equation can be rearranged to give:

$$\text{Force} = \text{Pressure} \times \text{Area}$$

showing that for a given force, pressure and area have a reciprocal relationship.

Using an everyday example, when a constant and equal force is applied to two syringes of differing sizes, it is much harder to inject from the larger (e.g. 20ml) syringe compared to a smaller syringe (e.g. 2ml). This is due to the larger area of the plunger in the 20ml syringe. As already discussed, pressure and area have a reciprocal relationship so in the larger syringe, with the larger area, the pressure generated will be less. This reduced pressure results in the relative difficulty in injecting from a 20ml syringe.

Although the pascal is the SI unit of pressure, many other units of pressure measurement exist. Table 1 provides a comparison.

Table 1. Units of pressure

Unit of pressure	Amount equating to 1 atmosphere	Example of use
kPa	101.3	Gas cylinder pressure
pounds per square inch	14.69	Car tyre pressure
centimetres of water (cmH_2O)	1033	Airway pressure
bar	1.013	Gas cylinder pressure
millimeters of mercury (mmHg)	760	Blood pressure

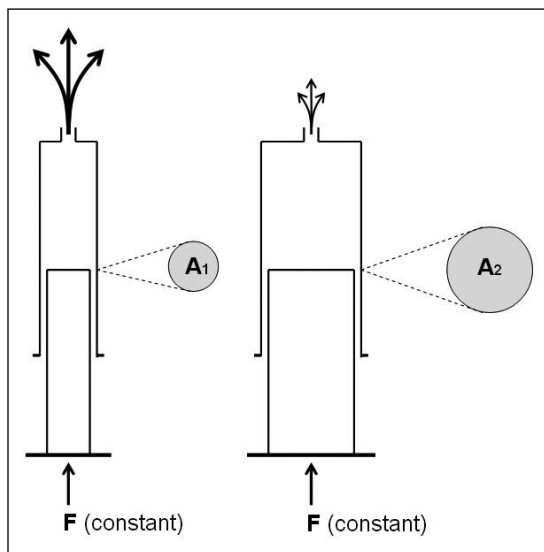


Figure 1. Injection from small and large syringes.
Force = force, A = area

GAUGE PRESSURE AND ABSOLUTE PRESSURE

Absolute pressure = gauge pressure + atmospheric pressure.

A full oxygen cylinder has a gauge which will read a pressure of 13700kPa. As the oxygen is used the pressure will fall until the gauge reads a pressure of 0kPa. However, at this point, unless a vacuum has been used to 'suck' oxygen out of the cylinder, it will still contain oxygen at the ambient atmospheric pressure (100kPa).

Therefore gauge pressures measure the pressure in a system above or below ambient atmospheric pressure. The majority of pressures measured by anaesthetists are gauge pressures and examples include gas cylinder pressures, blood pressure and ventilator pressures.

Summary

This article describes the basic science of pressure, its relevance to anaesthesia and critical care, and its measurement. Adequate blood pressure is essential to maintain the blood supply and function of vital organs. Measurement of blood pressure is therefore a key part of the monitoring of patients during anaesthesia and critical care.

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Given the above equation the absolute pressure of an oxygen cylinder is 13800kPa when full.

PRESSURE MEASUREMENT

Many different systems can be used to measure pressures, some of which are outlined below. Each has advantages and disadvantages.

Manometers

Manometers are columns of liquid used to measure pressure, usually limited to pressures near to that of the atmosphere. Pressure is measured by its ability to displace the column of liquid in the manometer. The column will rise or fall until its weight is in equilibrium with the pressure difference between the two ends of the tube. A simple version is a U-shaped tube (Figure 2), half filled with liquid, one end of which is exposed to atmospheric pressure and the other exposed to the pressure to be measured.

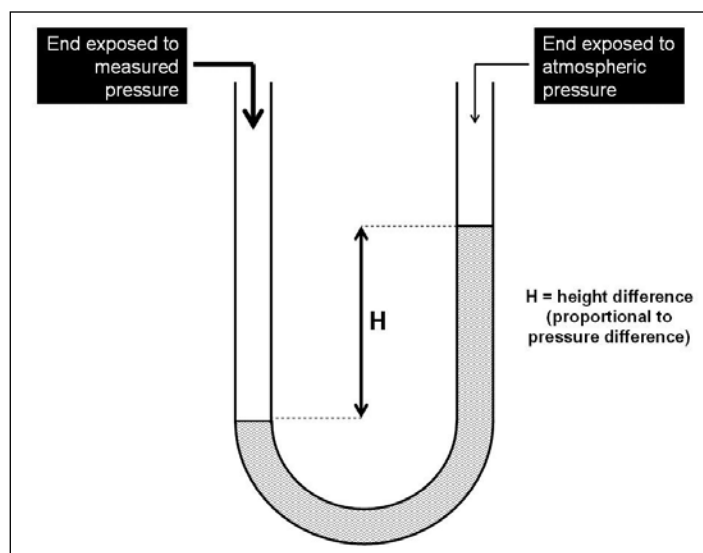


Figure 2. A manometer

The commonest liquids used are water and mercury, each having their own advantages. Mercury is 13.6 times denser than water and hence can be more easily used to measure higher pressures. The pressure in the column is equal to the product of the height of the column, the liquid's density and the force of gravity. The width, shape or even angulation of the column, have no impact on the pressure reading.

Surface tension has an effect on the meniscus at the top of the liquid column. It will pull water up the walls of the tube causing a slight over-reading, whilst in a mercury manometer the meniscus is convex and the level of the liquid is depressed.

Bourdon gauge

This pressure measurement device is used for the measurement of high pressures, where the required height of the fluid column in a manometer would be impractical. A Bourdon gauge uses a coiled tube which, as it expands due to increased pressure, moves a pointer over a scale.

A bourdon gauge is an example of an *aneroid* gauge meaning 'without fluid'. Another type of aneroid gauge is based on a bellows mechanism, the bellows expanding with increased pressure. These

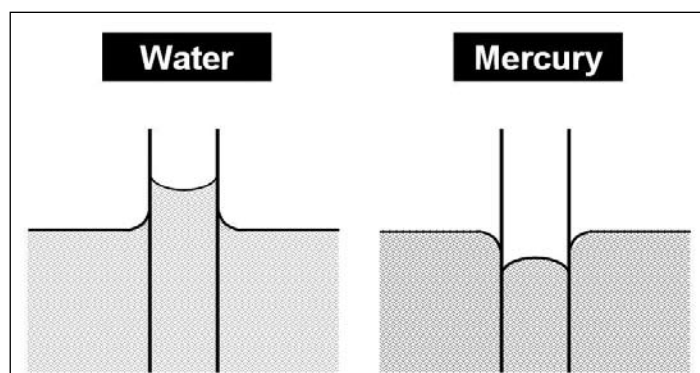


Figure 3. Menisci of water and mercury

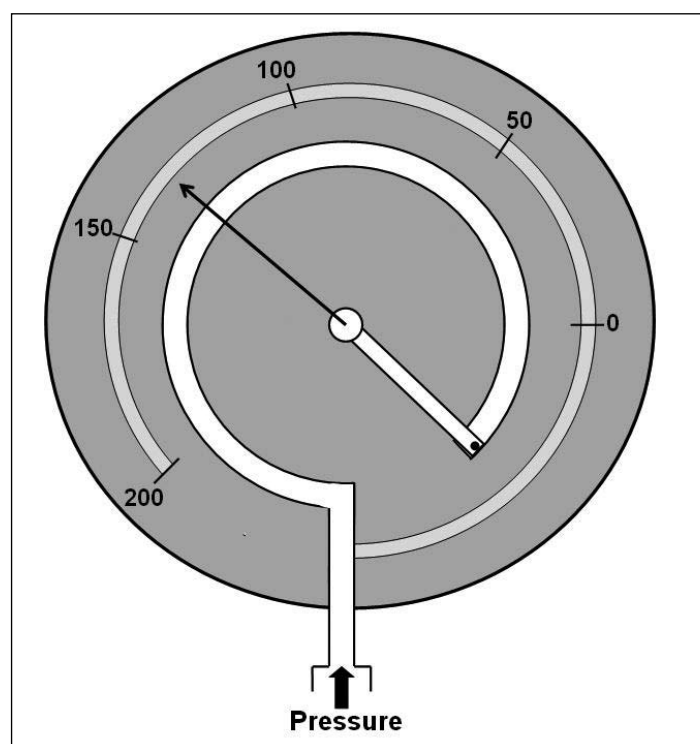


Figure 4. A bourdon gauge; as the pressure increases the coil unravels and indicates the pressure on the calibrated scale. A system of cogs (not shown in this figure) converts uncoiling of the coil into clockwise movement of the needle

are useful for the measurement of small pressures and can be open to the atmosphere (and measure gauge pressure) or closed (and measure absolute pressure).

Diaphragm

Another type of aneroid gauge is a diaphragm. This uses a flexible membrane which is deflected by changes in pressure. The amount of deflection is proportional to the pressure and hence the pressure can be determined once the system used has been calibrated. These are commonly found in systems used to measure direct intra-arterial blood pressure.

MEASUREMENT OF BLOOD PRESSURE

What is normal blood pressure?

'Normal' or 'acceptable' blood pressure varies with age, state of

health and the clinical situation. At birth, a typical blood pressure is 80/50mmHg. It rises steadily throughout childhood, so that in a young adult it might be 120/80mmHg. As we get older, blood pressure continues to rise and a rule of thumb is that normal systolic pressure is [age in years + 100] mmHg. Blood pressure is lower in late pregnancy and during sleep.

Therefore a systolic pressure of 160mmHg for an elderly man or 90mmHg for a pregnant woman may be quite normal. To judge whether any particular reading is too high or too low, it must be compared to the 'normal' blood pressure for that patient.

TECHNIQUES OF MEASUREMENT OF BLOOD PRESSURE

Rough estimates (no equipment available)

It is not possible to derive a numerical value for blood pressure without some equipment, but a crude assessment of the circulation can still be obtained. If you can feel a radial pulse, the systolic blood pressure is usually at least 80mmHg. The character of the pulse, i.e. bounding or thready, gives a further clue. In most cases, shocked patients have cold hands and feet - the most important exception to this is a patient who is shocked because of severe sepsis.

Capillary refill time is another simple test of circulatory adequacy: press firmly on the patient's nail bed with your thumb for 3 seconds; release your thumb and see how long it takes for blood to return. A refill time of greater than 2 seconds suggests an inadequate circulation. This test is particularly useful to diagnose shock and monitor the response to fluid therapy in children - the skin over the chest wall is a common site for this.

Manual non-invasive blood pressure measurement

This requires, at the very least, an inflatable cuff with a pressure gauge (sphygmomanometer). Wrap the cuff round the arm (which should be at about heart level) and inflate it to a pressure higher than the expected blood pressure. Then deflate the cuff slowly. With a stethoscope, listen over the brachial artery. When the cuff reaches systolic pressure, a clear tapping sound is heard in time with the heart beat. As the cuff deflates further, the sounds initially become quieter, but then become louder again before disappearing altogether. The point at which the sounds disappear completely is the diastolic pressure. If you have no stethoscope, the systolic blood pressure can be estimated by palpating the brachial artery and noting the occlusive pressure in the cuff at which it becomes palpable.

The sounds described above are called the *Korotkoff sounds* and undergo 5 phases:

- | | |
|-----|---|
| I | initial 'tapping' sound (cuff pressure = systolic pressure) |
| II | sounds increase in intensity |
| III | sounds at maximum intensity |
| IV | sounds become muffled |
| V | sounds disappear (diastolic pressure) |

Most inaccuracies result from the use of the wrong size of cuff. A narrow cuff wrapped round a broad arm will give a falsely high reading and vice versa. The World Health Organisation recommends a 14cm

width cuff for use in adults. Smaller cuffs for infants and children are available. Occasionally, the reading obtained from one arm may be different from that obtained from the other arm - this is usually of no clinical relevance, but can be an indication of aortic pathology, notably dissection or coarctation.

An appropriate size of cuff can be applied to the calf and pressure estimated by palpation of the posterior tibial pulse. This may be useful during surgery, when the patient's arms are away from the anaesthetist, e.g. shoulder surgery.

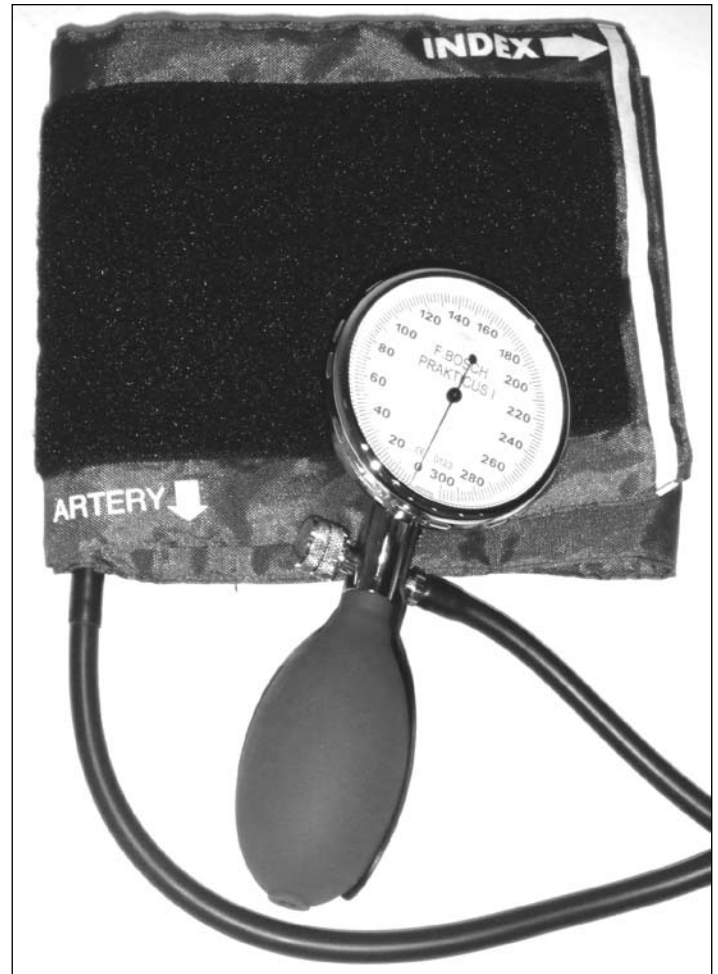


Figure 5. A simple non-invasive blood pressure device

Oscillotonometry

The Von Recklinghausen oscillotonometer is a device that allows both systolic and diastolic blood pressure to be read without a stethoscope. It consists of two overlapping cuffs (one large, one small), a large dial for reading pressure, a bleed valve and a control lever. The large cuff performs the usual function of the sphygmomanometer cuff. The job of the smaller cuff is to amplify the pulsations which occur as the larger cuff is deflated, so that instead of listening for the Korotkoff sounds, they are seen as oscillations of the needle on the pressure dial. The lever simply switches the dial between the two cuffs.

Technique of use for an oscillotonometer

- Wrap the cuff round the arm in the usual way, and inflate it.
- Adjust the bleed valve so that the pressure falls slowly.

- Pull the control lever towards you. The needle will jump slightly in time with the pulse.
- As the cuff pressure approaches systolic, the needle suddenly starts to jump more vigorously. At this point, let go of the lever, and the needle will display systolic pressure.
- Pull the lever forward again. As the pressure is reduced, the needle jumps more vigorously.
- If the lever is released at the point of maximum needle oscillations, the dial will read the mean arterial pressure.
- If it is released at the point when the needle jumps get suddenly smaller, the dial reads diastolic pressure.
- There are important sources of inaccuracy:
 - Such devices tend to over-read at low blood pressure, and under-read very high blood pressures.
 - The cuff should be an appropriate size.
 - The patient should be still during measurement.
 - The technique relies heavily on a constant pulse volume, so in a patient with an irregular heart beat (especially atrial fibrillation) readings can be inaccurate.
 - Sometimes an automatic blood pressure measuring device inflates and deflates repeatedly 'hunting', without displaying the blood pressure successfully. If the pulse is palpated as the cuff is being inflated and deflated the blood pressure may be estimated by palpation and reading the cuff pressure on the display.

Automatic non-invasive blood pressure measurement

Automatic devices, which essentially apply the same principle as the oscillotonometer, have been produced (e.g. the 'Dinamap' made by Critikon). They require a supply of electricity.

Technique of use

- A single cuff is applied to the patients arm, and the machine inflates it to a level assumed to be greater than systolic pressure.
- The cuff is deflated gradually. A sensor then measures the tiny oscillations in the pressure of the cuff caused by the pulse.
- Systolic blood pressure is taken to be when the pulsations start, mean pressure is when they are maximal, and diastolic is when they disappear.
- Readings are fairly accurate and a major advantage is that they free the hands of the anaesthetist for other tasks.

Invasive arterial pressure measurement

This technique involves direct measurement of arterial pressure by placing a cannula in an artery (usually radial, femoral, dorsalis pedis or brachial). The cannula must be connected to a sterile, fluid-filled system, which is connected to an electronic monitor via a transducer. The advantage of this system is that pressure is constantly monitored beat-by-beat, and a waveform (a graph of pressure against time) can be displayed. Patients with invasive arterial monitoring require very close supervision, as there is a danger of severe bleeding if the line becomes disconnected. It is generally reserved for critically ill patients or those undergoing major surgery, where rapid variations in blood pressure are anticipated. The basic science principles behind this technique of blood pressure measurement are described in the article, *Biological signals and their measurements*.

Biological Signals and their Measurement

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INTRODUCTION

Biological signals are electrical or magnetic signals generated by biological activity within the human body. They can be monitored directly using electrodes, for example the electrocardiogram (ECG) and electroencephalogram (EEG), or can be reproduced via a system incorporating a transducer, for example invasive blood pressure monitoring. The signals are amplified, manipulated, processed and then usually analysed by a computer. The end product is the biological signal converted into a readable form.

SYSTEMS MEASURING ELECTRICAL SIGNALS

Electrodes

An electrode is a solid electrical conductor through which an electrical current can enter or leave a medium, for example the human body. They are usually in direct contact with a tissue. Skin electrodes are usually silver metal coated in a thin layer of silver chloride, in contact with chloride gel on a spongy pad, which then comes into contact with skin.



Figure 1. Skin silver-silver chloride electrodes

THE ELECTROCARDIOGRAM (ECG)

This is the surface reflection of myocardial electrical activity. Electrical activity from the myocardium is measured as a voltage at a series of skin electrodes. The electrical potentials from the myocardium at the level of the myocyte are about 90mV, but by the time they have traversed the chest to reach the skin they are reduced to 1-2mV. Skin-electrode impedance also accounts for some of this reduction in voltage.

Impedance

Impedance is resistance to the flow of alternating current. The electrodes themselves create a small

amount of impedance due to the electrochemical properties of the electrode. Skin-electrode impedance is due to imperfect mechanical contact between the electrode and skin. If impedance is high, then the signal can be distorted by interference, often from the domestic mains supply or by muscle movement producing electrical activity in the muscle. To reduce skin resistance and improve the signal, the skin should be hairless, clean and dry.

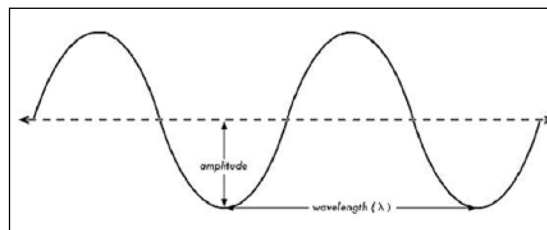


Figure 2. A typical sine wave. The frequency is the number of cycles, or complete sine waves, per second and the reciprocal of the wavelength. Hertz (Hz) is the standard unit of frequency

Sine waves

The ECG signal is actually a complex waveform made up of many different sine waves superimposed onto each other (Figure 2). A sine waveform is a description of a quantity that varies rhythmically with time. An example is the variation of voltage against time of an alternating current. Fourier analysis can be used to break down complex biological waveforms into their constituent individual sine waves. The slowest individual sine wave of the waveform is known as the *fundamental frequency*. Related sine waves that are multiples of the fundamental frequency are called the *harmonics*.

Bandwidth and amplification

Since the amplitude (or 'strength') of these types of biological signals is very small, they need to be *amplified* in order to be interpreted. Amplification describes the process of strengthening a signal, so that it is usable. During the amplification process, the frequency range of amplification (the *bandwidth*) must be sufficient to ensure that sufficient numbers of the *harmonics* of the signal are amplified, such that the amplified signal accurately represents the original unamplified signal. To

Summary

Biological signals are electrical or magnetic activity within the human body. They are usually detected via electrodes or transducers. Complex waveforms are reproduced using Fourier analysis. Transducers convert one energy form into another and can be used to monitor biological signals, for example blood pressure.

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be able to accurately reproduce the initial waveform, the bandwidth needs to be wide enough to include the fundamental and (usually) eight further harmonics.

The bandwidth for ECG amplification is 0.5-80Hz. A lower range would allow interference from movement and respiration, whereas higher frequencies would detect and amplify muscle movement and distortion from nearby equipment. For monitoring purposes the bandwidth can be reduced to 40Hz, which removes interference from mains current, but needs to be increased for ST segment analysis.

The ECG display

The ECG is displayed via an oscilloscope, usually moving at 25 mm.s⁻¹, or as a digital image with the same speed on the baseline. Depolarisation towards a lead causes a positive deflection and away from a lead causes a negative deflection (Figure 3). The size of the deflection is usually proportional to heart muscle bulk underlying that electrode.

Usually, for diagnostic purposes, ten electrodes are applied to the skin, one on each limb (the 'limb leads') and six across the anterior chest wall (the 'chest leads'). This arrangement gives twelve different waveform readings, the '12-lead ECG'.

The augmented unipolar and chest leads use a reference electrode by connecting all three augmented unipolar leads.

During anaesthesia, it is common to only use the three standard leads, with lead II being superior for detection of arrhythmias. Other configurations of electrodes include 'CM5', which is better at detecting left ventricular ischaemia. The right arm electrode is placed on the manubrium, the left arm at V5 position and the third lead on the left shoulder.

THE ELECTROMYOGRAM (EMG)

The EMG is used to measure spontaneous or evoked potentials from muscles. Needle electrodes can be inserted into the muscles or surface electrodes can be used. The patient can either carry out a movement to

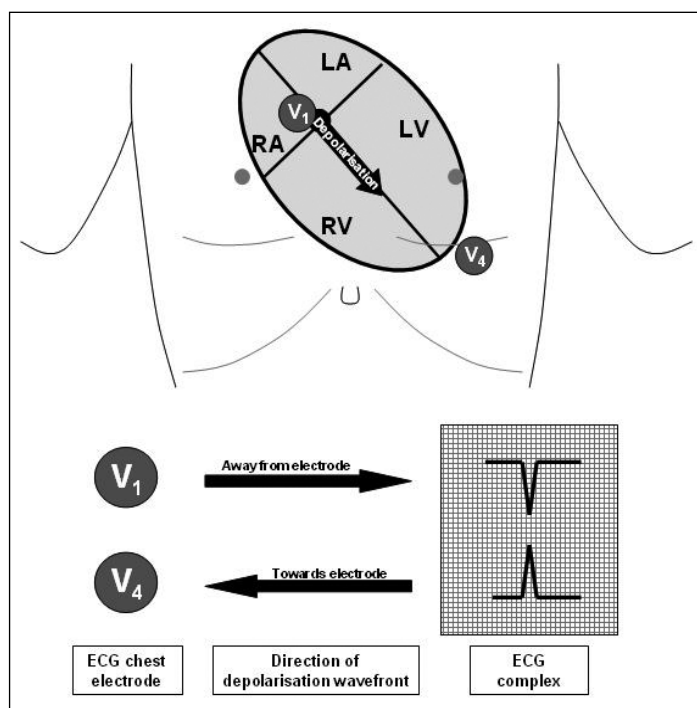


Figure 3. Diagram to show how electrode position determines the polarity of the ECG trace during depolarisation of the heart muscle (here depolarisation travelling from the AV node through the interventricular septum towards the apex of the heart). Lead V1 is over the right fourth intercostal space and lead V2 is over the apex of the heart

elicit a spontaneous potential, or the nerve supplying the muscle can be stimulated. The measured potentials range from less than 50mcV up to 20-30mV. The bandwidth of the amplified signal is much larger than the ECG, with a range of 0-4kHz.

Clinically, the principle of the EMG can be used for monitoring neuromuscular blocking drugs. A nerve stimulator is used to apply a supramaximal current to a nerve to ensure depolarisation. The

Table 1. Standard lead positions. The chest leads are positioned as indicated. The standard and augmented unipolar leads are derived from the readings of four leads attached to the patient's limbs

Standard leads	I	Between right and left arm
	II	Between left leg and right arm
	III	Between left leg and left arm
Augmented unipolar leads	aVR	Right arm
	aVL	Left arm
	aVF	Left leg
Unipolar chest leads	V1	Right parasternal, 4th intercostal space
	V2	Left parasternal, 4th intercostal space
	V3	Between V2 and V4
	V4	Over apex
	V5	At level of V4 in anterior axillary line
	V6	At level of V4 in mid-axillary line

muscle response is commonly detected visually, but it can be detected electrically and more accurately by EMG. EMG is also used for nerve conduction studies to diagnose myopathic and neuropathic disorders, which patients in the intensive care unit may develop.

THE ELECTROENCEPHALOGRAM (EEG)

The EEG measures the electrical activity of the brain using skin electrodes. Monitoring brain activity usually uses 21 electrodes for diagnostic purposes in the internationally recognised '10-20 system'. The EEG detects the sum of post-synaptic potentials from the pyramidal cells in the cerebral cortex in response to rhythmic discharges from thalamic cells.

The EEG waveforms vary with frequencies ranging up to 40Hz. The amplitude of the waveforms can be between 1 and 100mcV. The frequencies are often divided into bands:

- Alpha: 8-13Hz
- Beta: 13-40Hz
- Theta: 4-7Hz
- Delta: <4Hz

All the frequency bands can be normal in some situations but pathological in others. For example, alpha rhythms are seen during rest with the eyes closed, especially over the parieto-occipital region (Figure 4), but are also seen in coma where they represent deactivation. Delta bands can be a sign of an intracranial lesion, but are normal in babies.

The EEG has a number of clinical applications and is useful in the Intensive Care Unit (ICU) to diagnose seizure activity, particularly when the clinical picture is unclear (for example in 'non-convulsive status epilepticus'). Anaesthetic drugs affect the EEG. As the level of anaesthesia increases, the frequency of the EEG waveforms decreases dose-dependently until, at very high doses, the frequencies are very low, with suppressed amplitude and occasional bursts of higher frequencies with high amplitudes. *Burst suppression* is when there are absences of these high frequency episodes and is taken as the desired end-point to minimise the cerebral metabolic rate, when treating patients in the ICU with intractable intracranial hypertension. Smaller doses can cause an increase in frequency and activity, with mainly beta bands detected.

During clinical anaesthesia the picture may be complicated by other conditions that alter brain activity, for instance hypoxia and hypercarbia. In addition, different anaesthetic drugs produce different EEG characteristics.

BISPECTRAL INDEX MONITORING (BIS)

Full EEG monitoring is impractical in theatre and bispectral (BIS) index monitoring has superseded other methods for monitoring depth of anaesthesia. The EEG signal can be modified and an algorithm used to generate a number that represents a level of consciousness between 0 (very deep) and 100 (fully awake). BIS has been validated on healthy volunteers and different patient groups but there is no gold standard for comparison. A single pair of electrodes is applied to the patient's forehead as in Figure 5.

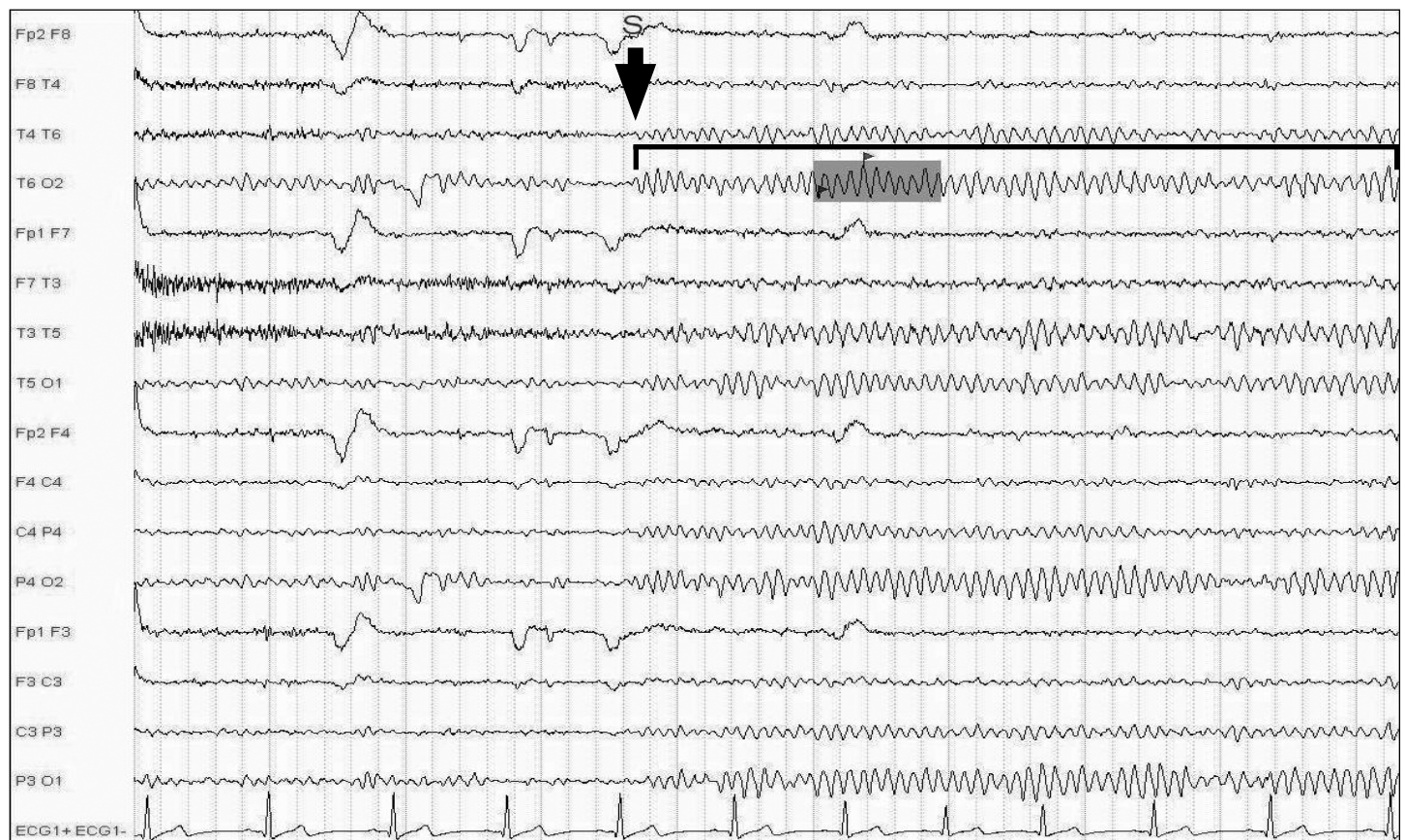


Figure 4. A normal EEG. The arrow indicates when the patient's eyes are closed and alpha rhythms (bracketed) are seen



Figure 5. Electrode positions for bispectral index monitoring (BIS)

The BIS index algorithm uses power spectral analysis and time-domain analysis. It also examines the relationship between the individual frequency components to each other (phase coupling). Time-domain analysis was developed as part of a 'cerebral function monitor' in the 1950s in order to measure changes in amplitude and frequency of brain signals over time. Power spectral analysis uses frequency-domain analysis, where wave amplitudes are measured and taken as an indication of 'power' within each frequency of the EEG. Power is plotted versus frequency, and each frequency is considered individually.

Table 2. Suggested interpretation of BIS values

BIS value	Interpretation
100-85	Awake, aware and capable of recall
85-60	Increasing sedation but rousable in response to stimulation
60-40	Surgical anaesthesia with decreasing probability of post-operative recall
40-0	Increasing incidence of burst suppression
0	Cortical electrical silence

BIS is thought to be independent of the anaesthetic drug given and correlates with clinical assessment of consciousness. One major disadvantage of BIS is that effects on consciousness due to opioids, ketamine and nitrous oxide are not reflected in BIS values. It is thought that the probability of post-operative recall is low if the BIS value is less than 60 intraoperatively. Studies have demonstrated that BIS monitoring intraoperatively reduces the risk of post-operative recall (as does the use of a volatile agent in the range 0.7-1.3 MAC in the presence of nitrous oxide).

SYSTEMS INCORPORATING A TRANSDUCER

Transducers convert one form of energy into another. With biological signals, transducers convert physiological signals into electrical signals, which can be then interpreted.

INVASIVE BLOOD PRESSURE (IBP) MEASUREMENT

Components and principles of IBP monitoring

The components of an intra-arterial monitoring system can be considered in three main parts (see Figure 6):

1. The measuring apparatus,
2. The transducer,
3. The monitor.

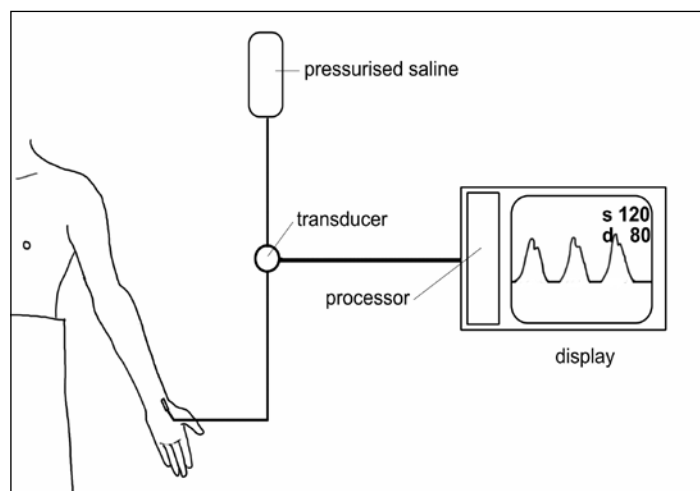


Figure 6. Components of an arterial monitoring system

The measuring apparatus

The measuring apparatus consists of an arterial cannula (20G in adults and 22G in children) connected to tubing containing a continuous column of saline that conducts the pressure wave to the transducer. The arterial line is also connected to a flushing system consisting of a 500ml bag of saline pressurised to 300 mmHg via a flushing device. Formerly 500IU heparin was added to this fluid, but many centres now consider this to be unnecessary. The flush system provides a slow but continuous flow to the system at a rate of approximately 4-5ml per hour. A rapid flush can be delivered by manually opening the flush valve. There is also usually a 3-way tap to allow for arterial blood sampling and the ejection of air from the system if necessary. The three-way tap must be clearly labelled as arterial to avoid the inadvertent intra-arterial injection of drugs. For small children a smaller volume of flush is administered via a syringe driver, so that it is not possible to over-administer fluid by repeated flushing of the arterial cannula.

The transducer

A transducer is any device that converts one form of energy to another – for example, the larynx is a type of physiological transducer (air flow is converted to sound). The output of transducers is usually in the form of electrical energy. In the case of intra-arterial monitoring the transducer consists of a flexible diaphragm with an electric current applied across it (Figure 7). As pressure is applied to the diaphragm it stretches and its resistance changes, altering the electrical output from the system. The transducers used are differential pressure transducers and so must be calibrated relative to atmospheric pressure before use.

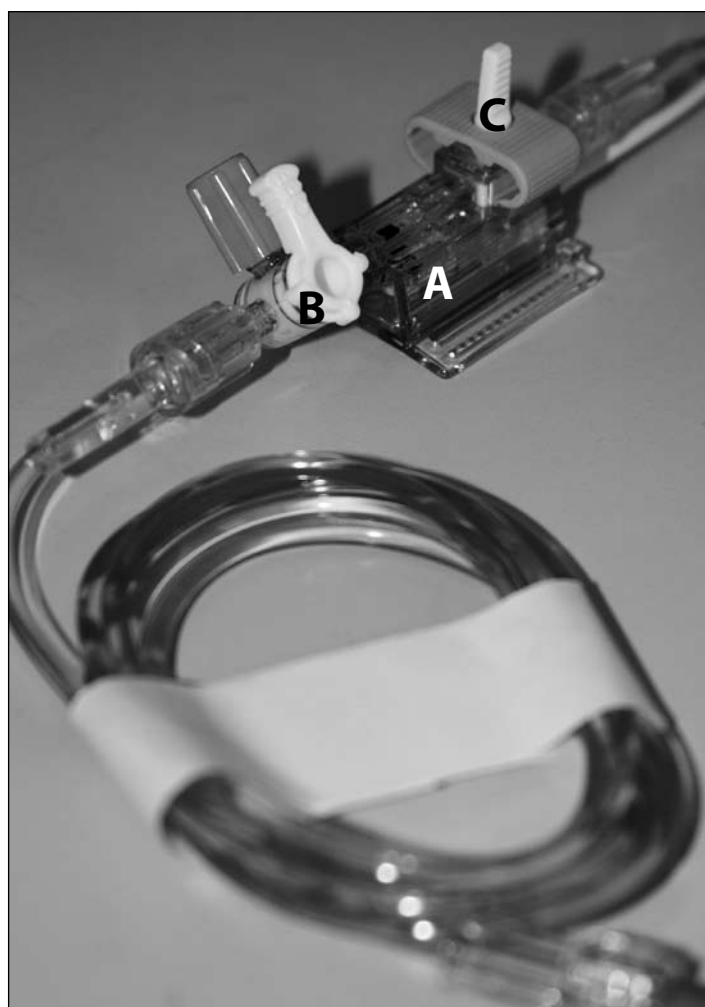


Figure 7. The transducer (A) of an arterial monitoring system, with a three way tap (B) for zeroing against atmospheric pressure and flushing device (C)

The monitor

It is not necessary for the anaesthetist to have an in-depth understanding of the internal workings of the monitor. Modern monitors *amplify* the input signal; amplification makes the signal stronger. They also *filter* the 'noise' from the signal – unwanted background signal is removed with an electronic filter - and display the arterial waveform in 'real time' on a screen. They also give a digital display of systolic, diastolic and mean blood pressure. Most monitors incorporate various safety features such as high and low mean blood pressure alarms and tachycardia and bradycardia alerts.

Accuracy of IBP monitoring

The accuracy of intra-arterial monitoring is affected by several important physical principles - the *oscillation*, *natural frequency*, *damping* and *resonance* of the system

Oscillation

A swinging pendulum is an example of a system that oscillates. When a pendulum is pushed (energy is put into the system), it moves away from its resting position, then returns to it. The resting position for a pendulum is at the bottom of its arc of swing and is dictated by gravity.

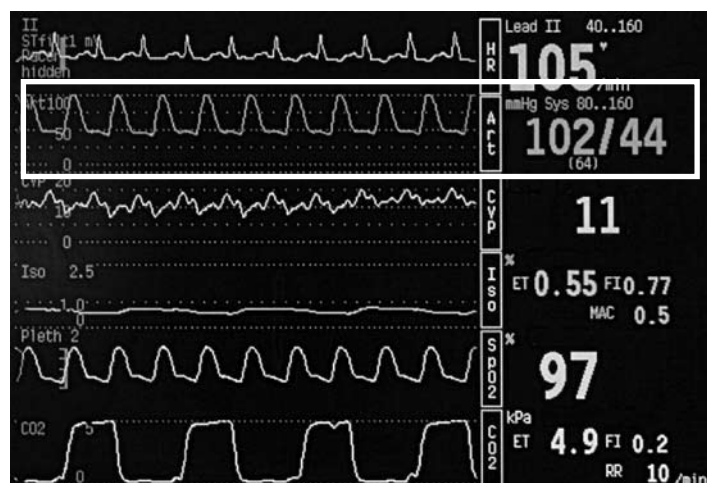


Figure 8. Invasive blood pressure monitoring (boxed). The waveforms are usually colour coded (red for the arterial trace) and the monitor displays the systolic/diastolic BP, with the mean arterial BP in brackets below

However, the pendulum doesn't usually just return to the resting position, but tends to overshoot, swinging past the resting point in the opposite direction to the original push. This cycle continues until all the energy put into the system has been dissipated. The tendency of a system to move either side of set point is referred to as its tendency to *oscillate*.

Damping

Imagine you have two identical pendulums. One has recently been well greased at its point of rotation (fulcrum) and the other is stiff from rust. When an equal sized force is applied to each, the well greased one will oscillate freely around the set point but the old rusty pendulum may barely move. This is because much of the energy put into the system will be used up or 'damped' in overcoming the frictional force of the rusty axis. The rusty pendulum will tend to oscillate at smaller amplitude (i.e. smaller swings) and for a shorter period of time than the well greased one. How freely a system oscillates following an input of energy depends on the degree of *damping* in the system.

A 'well damped' system tends not to oscillate freely whereas a 'poorly damped' system may oscillate wildly. The amount of damping inherent in a system can be described by the *damping coefficient* (*D*), which usually lies between 0 and 1 (but can be greater than 1). A system with a *D* value greater than 1 describes a system that is over-damped, will not oscillate freely, that takes a long time to initially move away from and to return to its resting point, but does not oscillate (a high friction pendulum). A *D* value less than 1 and approaching 0 describes a system that is under-damped, that oscillates freely, moving rapidly away from its resting point and back again, but tends to overshoot and then oscillate around the resting point (a low friction pendulum). A *D* value of exactly 1 is known as *critical damping*.

Oscillations are undesirable in physiological measuring systems. These systems require accurate measurement of a maximum amplitude (for instance, that caused by the arterial pulsation, the systolic blood pressure), with a rapid response time and rapid return to the set point, ready for the next measurement. The ideal level of damping applied to a measuring system is a compromise between achieving a rapid response time and accurate reflection of maximum amplitude by designing a

system with D close to 0, and needing a system that returns to the resting point without excess oscillation (D around 1). In the case of an IBP monitoring system this would represent the difference between using very compliant measuring apparatus (compliant catheters, tubing) i.e. D approaches 0, and very stiff or non-compliant equipment i.e. D is closer to 1. The value of D chosen for physiological measuring systems such as IBP monitoring equipment lies between 0.6 and 0.7 – it is known as *optimal damping* (see Figure 9).

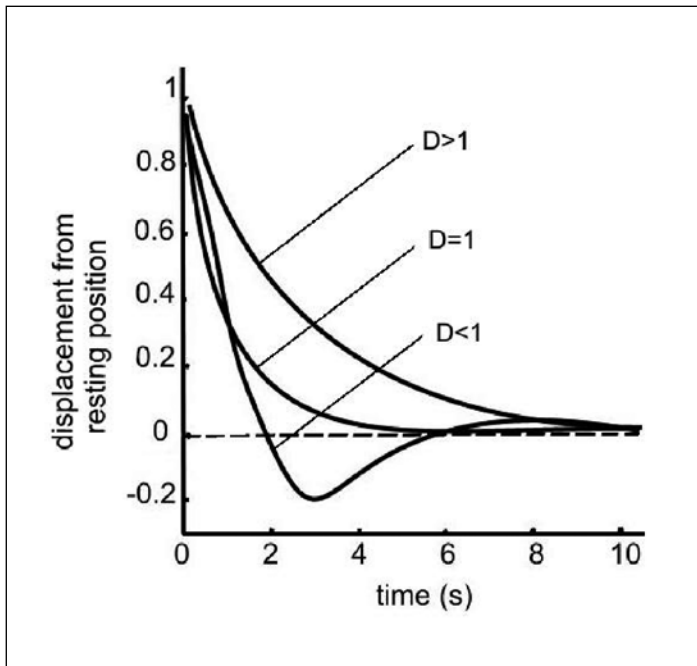


Figure 9. Graph showing the effect of different levels of damping on the oscillation of a measuring system

Natural frequency and resonance

A pendulum of set length and with a set weight at the end will always oscillate at exactly the same frequency, no matter what the initial starting point of the oscillation. In other words, whether you give the

pendulum a small push or a really hard shove it will make the same number of oscillations per unit time (although the amplitude of the oscillations will differ). This is why pendulums can be used to keep time. Any system such as this will have a frequency at which it ‘naturally’ oscillates. This frequency is known as the *natural frequency*.

If the input of energy into a system is occurring at the same frequency (or close to) the natural frequency, a phenomenon called *resonance* occurs and the output amplitude of the oscillations is greatly magnified. In the case of intra-arterial blood pressure monitoring this could lead to over-reading of the systolic blood pressure. Arterial pulsation is a complex sine wave and is composed of many individual sine waves. It is therefore important that the natural frequency of the measuring equipment (the catheter and column of saline etc) does not correspond to any of the component frequencies of the arterial pulsation input. This is achieved by making sure that the natural frequency of the measuring system is raised above any of the component frequencies of the arterial sine waveform.

The characteristics of the measuring equipment that will ensure that the natural frequency of the system is higher than that of the arterial pulsation are:

- Arterial catheter must be short and with the maximum gauge possible,
- Column of saline must be as short as possible,
- The catheter and tubing must be stiff walled,
- The transducer diaphragm must be as rigid as possible.

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Respiratory Gas Analysis

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OXYGEN CONCENTRATION ANALYSERS

It is important to measure the oxygen concentration in the gas mixture delivered to a patient during anaesthesia. There are three main techniques available for measurement of the inspired oxygen concentration (FiO_2): galvanic, polarographic and paramagnetic techniques. The paramagnetic method is currently the most widely used in modern anaesthetic machines, however galvanic fuel cells and the polarographic electrode are found in older machines. These analysers measure the oxygen partial pressure in a gas sample but they display a percentage. Regular calibration of oxygen analysers is vital.

Paramagnetic oxygen analysers

Oxygen possesses the property of *paramagnetism*, which means that it is weakly attracted into a magnetic field. This is because it has two electrons in unpaired orbits. Most of the gases used in anaesthesia are repelled by a magnetic field (diamagnetism).

The sample gas, taken from the breathing circuit, is delivered to the analyser via a sampling tube, which should be placed as close as possible to the patient's airway. Older paramagnetic analysers used a principle described by Figure 1.

Newer analysers have two chambers separated by a sensitive pressure transducer. The sample gas is delivered to one chamber and room air is delivered to the reference chamber. An electromagnet is rapidly switched on and off creating a changing magnetic field to which the sample gas is subjected. The magnetic field causes the oxygen molecules to be attracted and agitated. This results in changes in pressure on either side of the pressure transducer. The pressure difference across the transducer is proportional to the oxygen partial pressure difference between the sample gas and the reference gas (room air, containing 21% oxygen).

Paramagnetic oxygen analysers are very accurate and highly sensitive. The analysers should function continuously without any service breaks. They have a rapid response allowing measurement of inspiratory and expiratory oxygen on a breath-to-breath basis. They are affected by water vapour and have a water trap incorporated into their design.

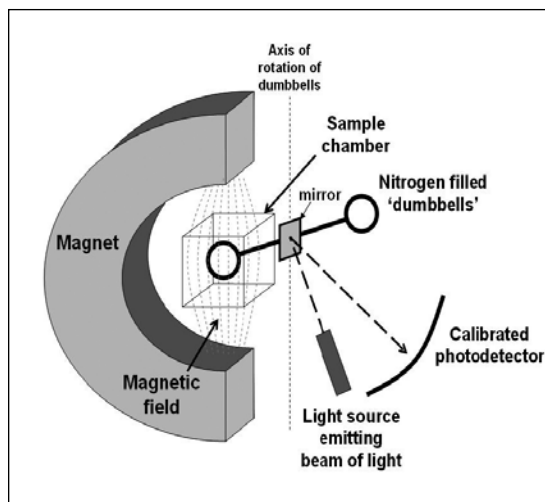
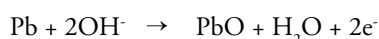


Figure 1. A paramagnetic analyser. The sample gas fills the sample chamber. Oxygen in the sample is attracted into the magnetic field and tends to displace the nitrogen filled dumbbell, which has no paramagnetic properties. The greater the concentration of oxygen present, the greater the displacement of the dumbbell. The degree of rotation of the pair of dumbbells is recorded by the amount a light beam is deflected, by a mirror mounted on the dumbbell axis

The galvanic oxygen analyser (Fuel cell)

The galvanic analyser is placed on the inspiratory limb of the breathing system (Figure 2). Oxygen molecules diffuse across a membrane and an electrolyte solution, to a gold (or silver) cathode, which is connected through the electrolyte solution to a lead anode. An electrical current is generated which is proportional to the partial pressure of oxygen in the inspired gas. The equation describing the reaction is:



The galvanic analyser has a response time of approximately twenty seconds and is accurate to within 3%. Calibration is achieved using 100% oxygen and room air (21% oxygen). Water vapour does not affect its performance. It has the advantage that it is a battery and therefore self-powering, however it is depleted by continuous exposure to oxygen due to exhaustion of the cell, so limiting its life span to about one year.

Summary

Monitoring of respiratory gases is considered by most to be highly important for the conduct of safe anaesthesia. Monitoring of inspired oxygen levels ensures against delivery of hypoxic gas mixtures to the patient and is useful for titration of oxygen flow where oxygen supplies are limited. Capnography tells an anaesthetist a great deal about the clinical status of the patient, both in terms of their respiratory and cardiovascular systems. It also lowers the threshold for suspicion for rare but potential fatal pathologies such as malignant hyperpyrexia. In many settings agent monitoring is not available, but its value in detecting and avoiding harmful overdose of anaesthetic agents or awareness due to insufficient levels, mean that, ideally, it should be incorporated into all anaesthetist's practice.

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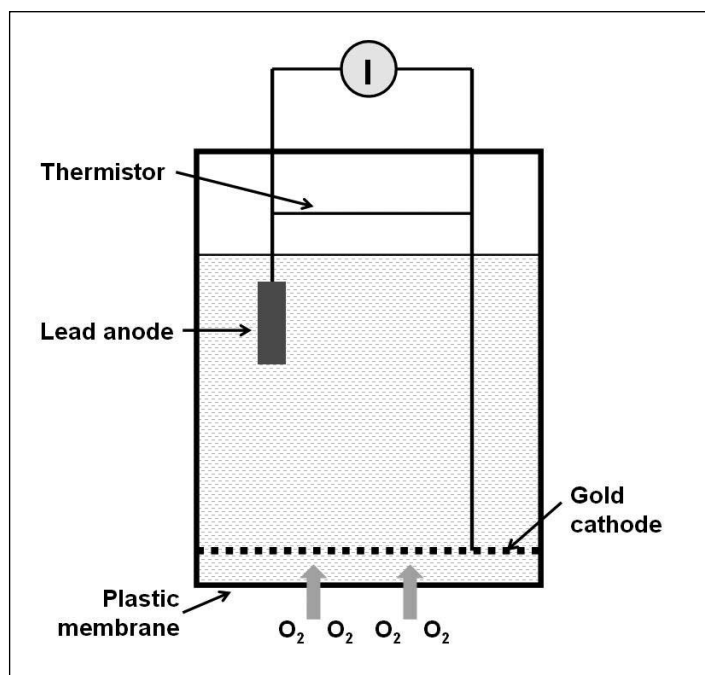


Figure 2. The galvanic oxygen analyser (Fuel cell)

The polarographic oxygen analyser (Clark electrode)

The polarographic analyser has similar principles to the galvanic analyser (Figure 3). Oxygen molecules diffuse across a teflon membrane. Current flows between a silver cathode and a platinum anode, which is proportional to the partial pressure of oxygen in the inspiratory gas. It is battery powered, but its life expectancy is limited to about three years because of deterioration of the teflon membrane.

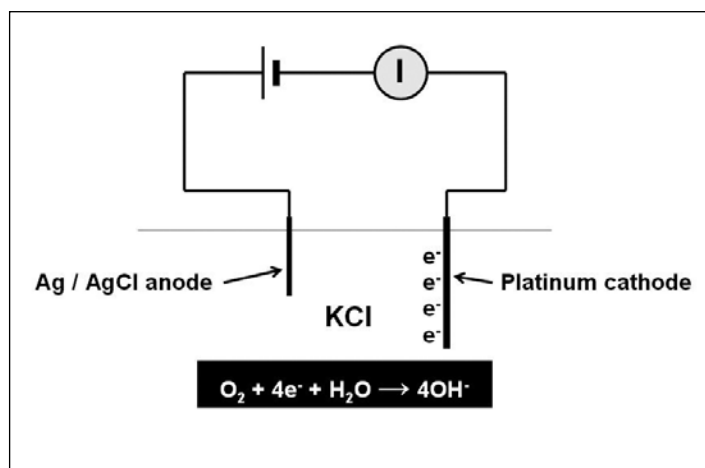


Figure 3. The polarographic oxygen analyser (Clark electrode)

CAPNOGRAPHY

Capnometry is the measurement of carbon dioxide (CO_2) and capnography is the display of the change in CO_2 level with the respiratory cycle. The capnograph displays a waveform of CO_2 - measured in kilopascals (kPa), millimetres of mercury (mmHg) or percentage - and also displays the numerical value of the CO_2 at the end of exhalation, the end-tidal CO_2 , which is the closest value to partial pressure of CO_2 in the alveolus or arterial blood.

It is useful to measure CO_2 to assess the adequacy of ventilation, to confirm tracheal intubation, to detect oesophageal intubation, to indicate disconnection of the breathing system or ventilator, and to diagnose circulatory problems and malignant hyperthermia.

Applications of capnography

Provided the patient has a stable cardiac status, stable body temperature, absence of lung disease and a normal capnograph trace, end-tidal carbon dioxide (ETCO_2) can be estimated to be about 0.5-1.0kPa below the partial pressure of CO_2 in arterial blood (PaCO_2). A normal PaCO_2 is about 5.3kPa (40mmHg). Note that the conversion factor between kPa and mmHg is 7.6.

Under the conditions described above, ETCO_2 can be used to assess the adequacy of ventilation - i.e. hypo-, normo-, or hyperventilation. ETCO_2 is not as reliable in patients who have respiratory failure. Any increased ventilation/perfusion (V/Q) mismatch is associated with a widened partial pressure (a-ET) gradient, and leads to ETCO_2 values that do not correlate with the true PaCO_2 .

The capnograph is the gold standard for detecting oesophageal intubation. No or very little CO_2 is detected if the oesophagus has been intubated.

The capnograph is also useful in the following circumstances:

- As a disconnection alarm for a ventilator or a breathing system. There is sudden absence of the capnograph trace.
- It may detect air embolism as a sudden decrease in ETCO_2 , assuming that the arterial blood pressure remains stable.
- To recognise sudden circulatory collapse as a sudden decrease in ETCO_2 .
- To diagnose malignant hyperthermia as a gradual increase in ETCO_2 .

Techniques of measurement

Most analysers in theatre work using two principles:

Infrared absorption spectroscopy

This is the most commonly used technique in anaesthesia. Gases of molecules that contain at least two dissimilar atoms absorb infrared radiation. Using this property, CO_2 concentration can be measured continuously throughout the respiratory cycle to give a capnograph trace. CO_2 absorbs infrared radiation particularly effectively at a wavelength of 4.3micrometers. A photodetector measures radiation reaching it from a light source at this wavelength. According to the Beer-Lambert Law, the amount of infrared radiation absorbed in the CO_2 sample chamber is proportional to the number of CO_2 molecules (partial pressure of CO_2) present in the chamber, and so the CO_2 concentration can be calculated.

Photo-acoustic spectroscopy

The sample gas is irradiated with pulsatile infrared radiation, of a suitable wavelength. Periodic expansion and contraction of the gas produces a pressure fluctuation of audible frequency that can be detected by a microphone. The advantages of photo-acoustic spectrometry over conventional infrared absorption spectrometry are:

- The photo-acoustic technique is extremely stable and its calibration remains constant over much longer periods of time.
- The very fast rise and fall times give a much truer representation of any change in CO₂ concentration.

Other techniques for measuring CO₂ include Raman scattering and mass spectrometry.

Raman scattering

When light passes through a gas sample it can undergo two types of reflective process:

1. *Rayleigh* scattering – where there is no change in the energy or frequency of the light,
2. *Raman* scattering – where the incident light loses energy to the molecules of the gas and is reflected at lower frequency (less than 1 millionth of the time).

The magnitude of the light frequency shift is specific to the gas and analysis of the reflected light allows identification of the gas. The light used is *intense, coherent and monochromatic* (i.e. from a laser). The machines are rapid, with breath to breath analysis, but tend to be bulky and heavy. They are more versatile than infra-red analysis and more reliable than mass spectrometry.

Site of sampling within the breathing system

Gas from the breathing system can be sampled either by a sidestream or a mainstream analyser.

Sidestream sampling

Gas is drawn from the breathing system by a 1.2mm internal diameter tube. The tube is connected to a lightweight adapter near the patient's end of the breathing system. It delivers the gas to the sample chamber. It is made of Teflon so it is impermeable to CO₂ and does not react with anaesthetic agents. Only the precise tubing recommended by the manufacturer should be used and only of the recommended length. Typical infrared instruments sample at a flow rate between 50 and 150ml.min⁻¹. When low fresh gas flows are used the sampled gas may be returned to the breathing circuit. It is important that the tip of the sampling tube should always be as near as possible to the patient's trachea, but the sampled gas mixture must not be contaminated by inspired gas during the expiratory phase.

Mainstream sampling

The sample chamber is positioned within the gas stream near the patient's end of the breathing system. Although heavier and more cumbersome, it does have advantages over sidestream sampling:

- The delay between the rise and fall times of gas composition changes and display on the capnograph is less, as gas does not need to be transported to the monitor.
- No gas is drawn from the breathing system.
- The mixing of gas that occurs along the sample tube with sidestream sampling is avoided.
- There are fewer problems with water vapour condensation.

The capnograph trace (Figure 4)

The first phase occurs during inspiration. The second phase is the onset

of expiration, which results in a rapid increase in the CO₂ reading. The third phase, the expiratory plateau, occurs as the CO₂ is exhaled from all of the alveoli. The highest point of the plateau is taken to represent the end-tidal CO₂ (ETCO₂). This marks the end of expiration. Phase four is the onset of inspiration.

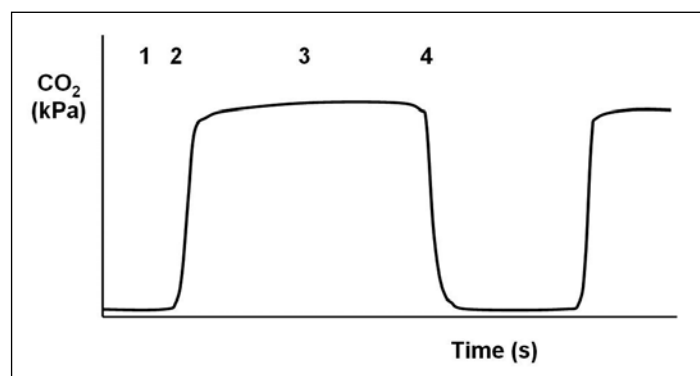


Figure 4. A typical capnography trace; 1 inspiratory baseline; 2 expiratory upstroke; 3 expiratory plateau; 4 inspiratory downstroke

Abnormal capnography traces

Rebreathing (Figure 5)

A waveform that does not return to the baseline during inspiration indicates rebreathing of exhaled CO₂-containing gas. Possible causes are:

- The fresh gas flow is too low in non-rebreathing system (e.g. Mapelson type A, D or E).
- The soda lime in a circle system is depleted.

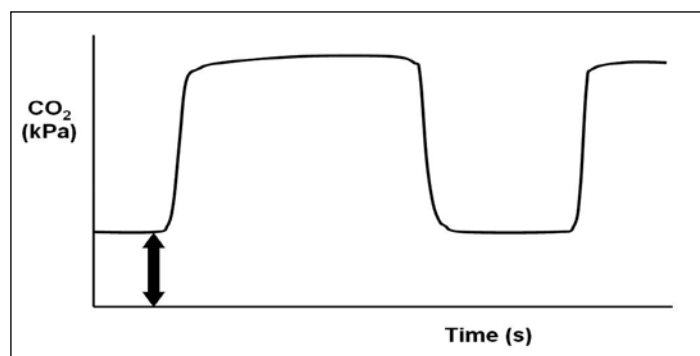


Figure 5. Rebreathing is indicated by failure of the trace to return to the baseline during inspiration (arrow)

Sloping plateau (Figure 6)

This appearance is seen in patients with obstructive airways disease (asthma and chronic obstructive pulmonary disease). In patients with obstructive airways disease, the lungs are perfused with blood as normal, but the alveoli are unevenly ventilated. CO₂ is transferred from the alveoli to the larger airways during expiration, but this takes longer in lung units that have narrower bronchi. These slower emptying lung units have a higher CO₂ concentration and so the CO₂ concentration in mixed expired gas gradually rises throughout expiration, as these slow emptying units contribute a greater proportion of the expired gas mixture.

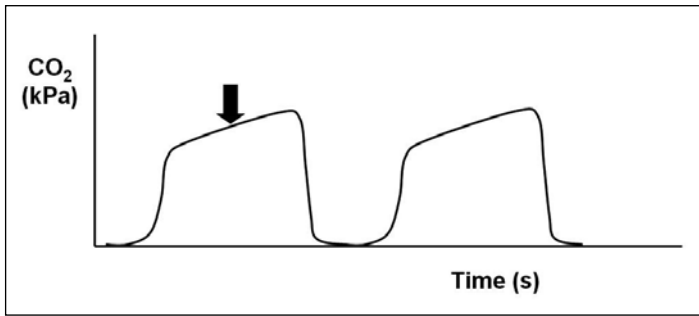


Figure 6. The sloping plateau (arrowed) is typical of lower airways obstruction (asthma and COPD)

Cardiac oscillations

Cardiac impulses are transmitted through the mediastinum to the large airways and are detected by the capnograph. These oscillations are most obvious in apnoeic patients, since the volume of gas that

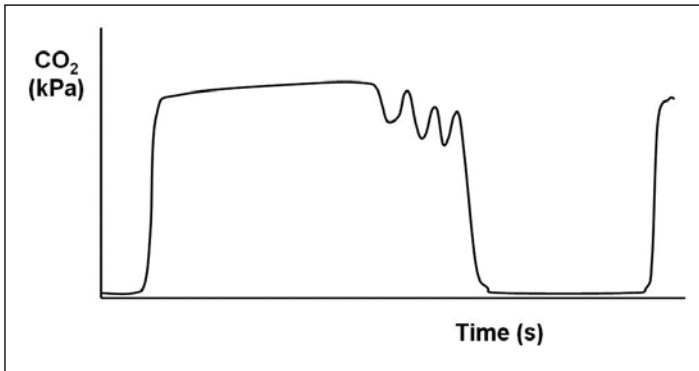


Figure 7. Cardiac oscillations.

they cause to move in the airways is a greater proportion of the overall lung volume when the patient is at functional residual capacity.

The 'curare cleft' (Figure 8)

This appearance indicates reversal of neuromuscular blockade in a ventilated patient. When a paralysed patient starts taking small breaths as the neuromuscular blocking agent reverses, clefts are seen on the capnograph trace.

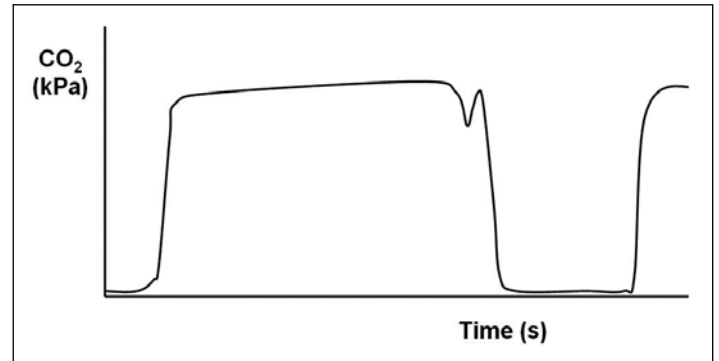


Figure 8. Breathing against the ventilator.

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Electricity and Magnetism

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ELECTRICAL CHARGE

Charge is a fundamental property of matter. Atoms, the fundamental particles that make up matter are composed of protons (with a positive charge), neutrons (with no charge) and electrons (with a negative charge). Electrons are 'point particles' with no physical substructure and they have properties characteristic of both a particle and a waveform. They are bound into atoms by their tendency to be attracted towards positively charged protons. Materials that are electrical conductors have loosely bound electrons in their outer shells.

ELECTRICAL CURRENT

Like *charges* repel and tend to move from sites of high charge density, or potential, to those with lower potential. Moving or flowing charge constitutes an electrical current and, as an aid to understanding this concept, the flow of current is roughly analogous to flow of fluids (Figure 1). By convention current is described as flowing from the positive electrode to the negative electrode, although in reality electrons (negatively charged) move in opposite direction (Figure 2).

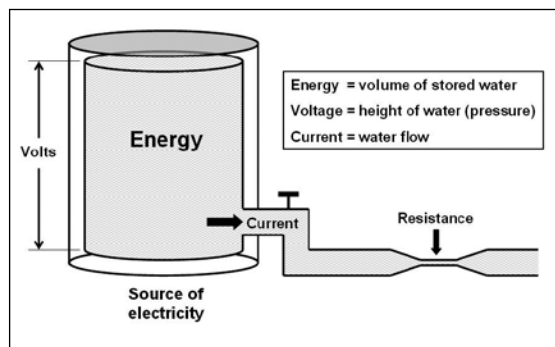


Figure 1. Electricity explained as an analogy to fluid flow

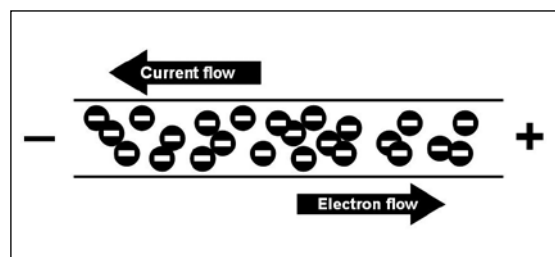


Figure 2. Conventional electric current flow and electron flow

DEFINITIONS AND UNITS

Ampere (A)

The unit of electrical current. *One of the seven fundamental SI units.*

Defined as the amount of current producing a force of 2×10^{-7} Newtons per meter (N.m^{-1}) between two infinitely long parallel conductors placed 1 meter apart in a vacuum.

Coulomb (C)

The unit of quantity of electrical charge.

Defined in terms of current flow per unit time or the quantity of charge carried past a point in one second by a current of 1A.

Volt (V)

The unit of electrical *potential*.

Defined as the difference of electrical potential between two points of a conductor carrying 1A current, when the power dissipated between the points is 1 watt (W).

Ohm (Ω)

The unit of resistance to flow of electrical current.

If a potential of 1V is applied across a conductor and the current flow is 1A, then the resistance is 1Ω .

STATIC ELECTRICITY

You may occasionally notice a click of energy when shaking someone's hand; this is due to build up of static charge by contact of our shoes on the carpet. The click is due to discharge of the static charge on contact with the other person. Static is a stationary collection of electrical charge that can be positive or negative. It is usually formed as a result of charge separation between dissimilar materials. Items are said to become charged, and a potential difference is created representing stored potential energy. This energy can be released or *discharged* as sparks, which has implications in theatre, particularly when using flammable agents such as ether.

CURRENT ELECTRICITY

Current describes moving electrical charge that flows around *circuits* and is described by Ohm's law:

$$\text{Current, } I = \frac{\text{Voltage, } V}{\text{Resistance, } R}$$

(or commonly rearranged as: $V = IR$)

Summary

This article outlines the areas of knowledge concerning electricity and magnetism that are essential for the practice of safe anaesthesia. The areas covered include basic concepts, amplification of biological potentials, sources of electrical interference, electrical hazards and their causes and prevention, diathermy and defibrillators.

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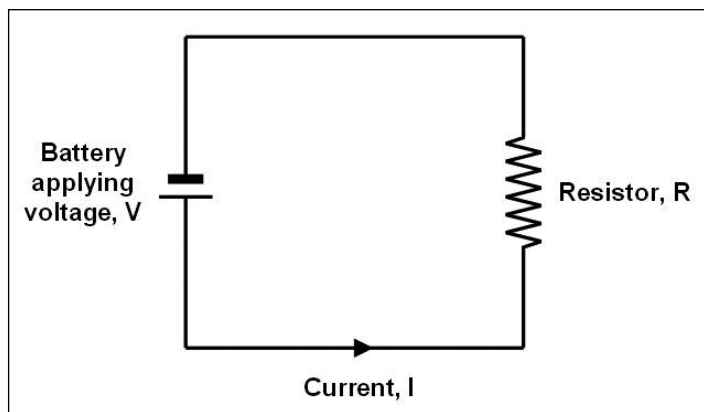


Figure 3. Ohm's law

Bridge circuits

Bridge circuits, for example the Wheatstone bridge, are used in equipment such as the transducer of an intra-arterial blood pressure system and are a simple application of Ohm's Law. Transducers change energy from one form to another – an arterial transducer responds to physical change (e.g. pressure causing stretch) by varying its resistance. A thermistor, which has a resistance that varies with temperature, is another example. A bridge circuit can be used to calculate the change in a physical quantity by measuring change in resistance of the transducer (Figure 4).

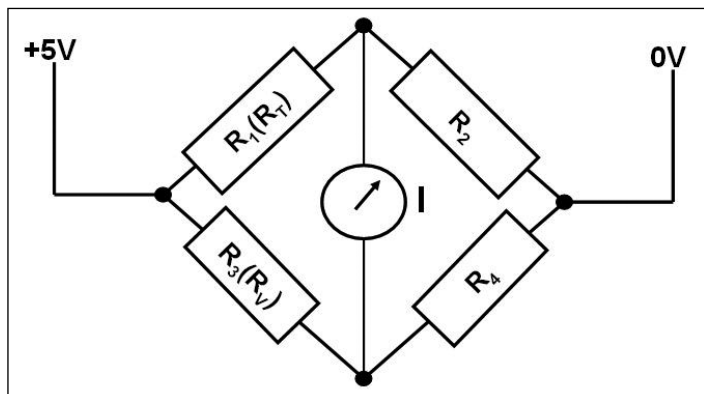


Figure 4. The Wheatstone Bridge. When $R_1/R_2 = R_3/R_4$, no current flows through the meter (I) and the 'bridge' is said to be 'balanced'. The transducer (R_T) is connected in place of R_1 and a variable resistor (R_V) replaces R_3 . The transducer is zeroed by adjusting R_V until there is no current flow through I. A change in the transducer's resistance unbalances the circuit and causes a current to flow through the meter. The amount that the variable resistor must be changed to restore the bridge to balance (i.e. no flow at I), can be used to calculate the resistance change at the transducer and therefore the pressure change to which the transducer has been exposed

Direct and alternating current

Direct current (DC) describes steady flow of current from a positive to negative pole. Almost all electronic equipment requires DC.

Alternating current (AC) is a sinusoidally oscillating flow of current produced as the potential between the poles reverses. Most electrical equipment runs on AC. United Kingdom mains is AC 240 volts, oscillating at (i.e. changing polarity at) a frequency of 50Hz (fifty times per second). The peak voltage is 340V. Because the voltage

oscillates symmetrically around zero, the average or mean voltage is zero. The figure of 240V is actually the root-mean-square (RMS) of the component values and gives a more meaningful figure for the average voltage (squaring the values, averaging them, then taking the square root makes the negative values, positive).

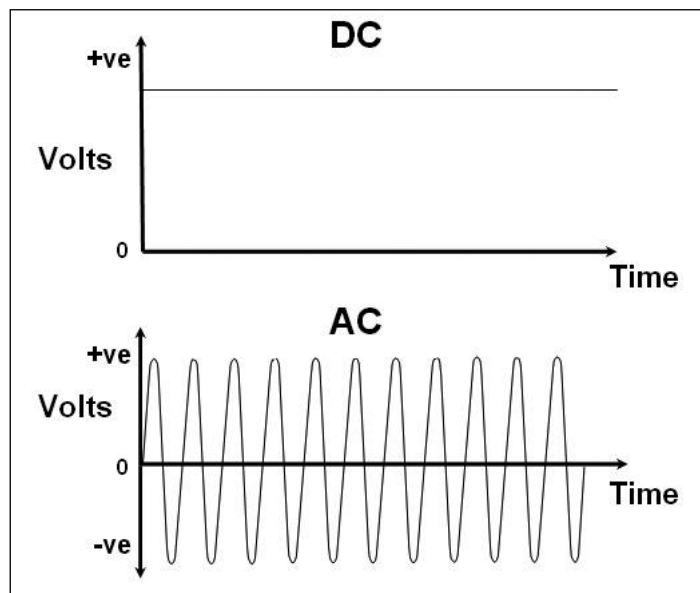


Figure 5. Graphical description of direct and alternating currents

MAGNETISM

Theory

Magnetic force is a fundamental natural force (like gravity) and, as such, is not easily explained. Magnetic poles are always paired and are usually described as *north* or *south*. Magnetic *fields* are classically described in terms of lines of flux, which show the direction of the magnet field at any particular point. Materials can be:

- **Ferromagnetic** – they are strongly attracted into a magnetic field, become magnetic while in the field and remain so after the field is removed,
- **Paramagnetic** – they are weakly attracted into a magnetic field,
- **Diamagnetic** – they are weakly repelled from a magnetic field.

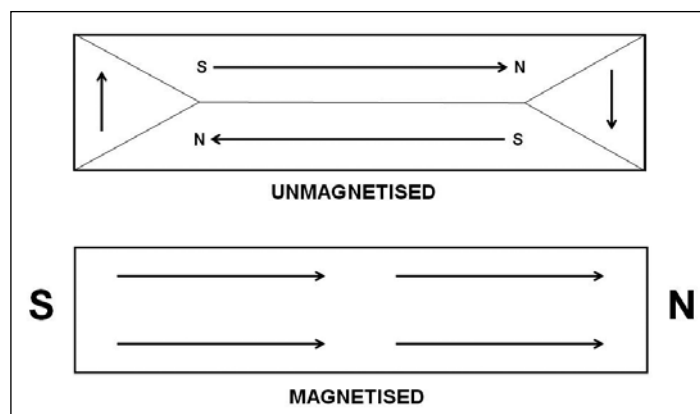


Figure 6. Ferromagnetism is described in terms of 'domains' – areas within the substance that are uniformly magnetised, with polarity in the same direction

Electromagnetism

Flow of electrical current and magnetism are inextricably linked. All moving charge (electrical current) produces a magnetic field. The *dynamo effect* means that if a conductor moves through a magnetic field, an electrical current will be *induced* in the conductor. Electromagnetism is governed by Flemings Rules - Figure 7.

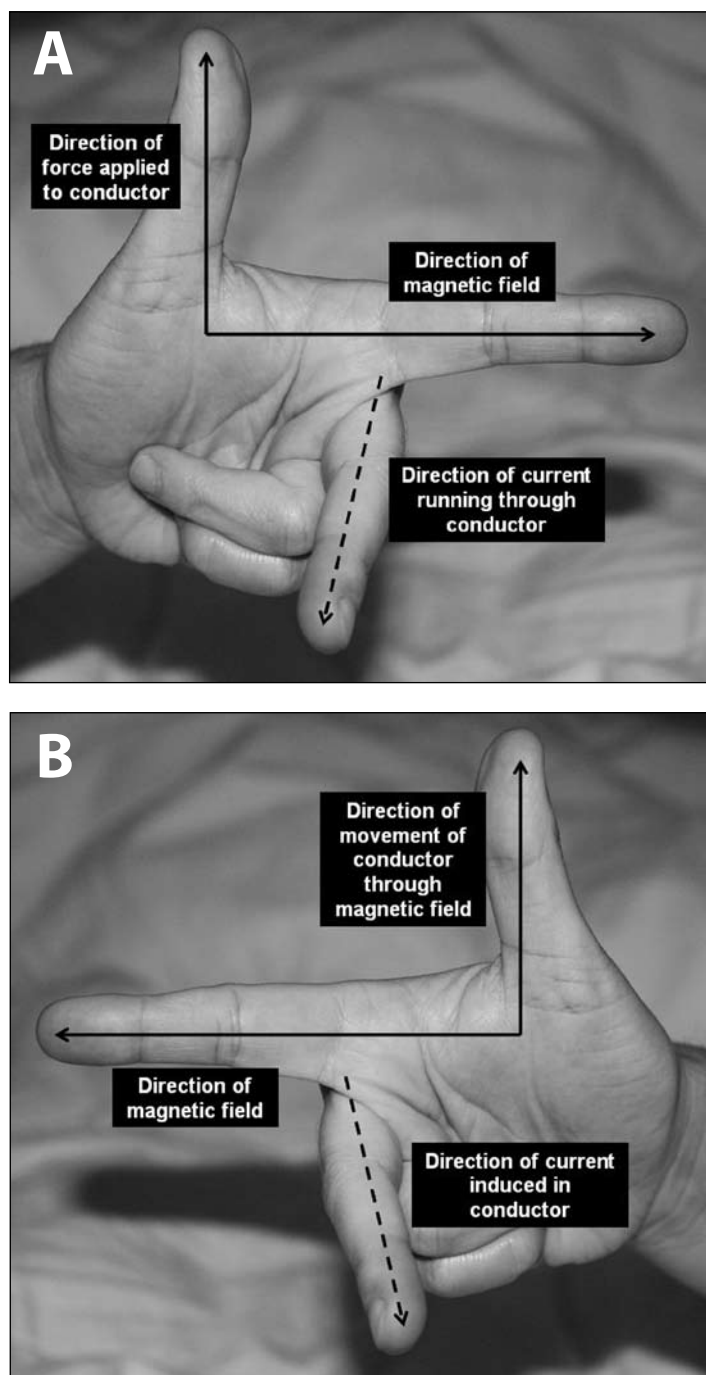


Figure 7. Flemings left and right hand rules of electromagnetic induction. The left hand rule (A) predicts the direction of Movement of a conductor (thumb), when a Current flows down it (in direction of second finger), in a magnetic Field in the direction of the First finger. The movement is driven by the induced electromotive force. The right hand rule (B) predicts the direction of current flow induced in a conductor moving through a magnetic field

Current flowing in a coil of wire produces a magnetic field within the coil and this is called an electromagnet or a *solenoid*. The magnetic field density generated is directly proportional to current flow and the number of turns of wire in the coil and is strongest within the solenoid (Figure 8). If the current is oscillating then an oscillating magnetic field is generated. Under certain conditions this oscillating field generates propagated electromagnetic waves - this phenomenon forms the basis of radio transmission.

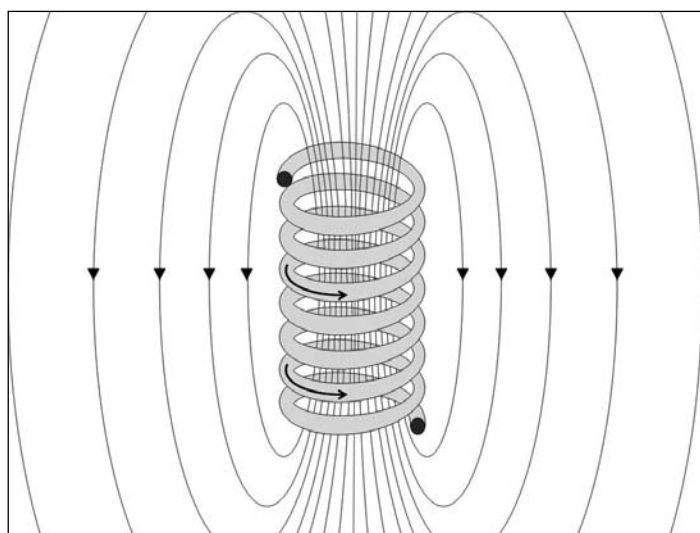


Figure 8. The magnetic field generated within a solenoid, with a current applied as indicated by the arrows

Applications of electromagnetism:

- Electric motors and dynamos,
- Transformers - step-up, step-down, isolating and signal transformers (see Figure 9),
- Solenoid valves - ventilators, gas mixers and safety interlocks,
- Magnetic 'springs' - e.g. the Bird ventilator,
- Paramagnetic oxygen analyzers,
- Magnetic resonance imaging (MRI).

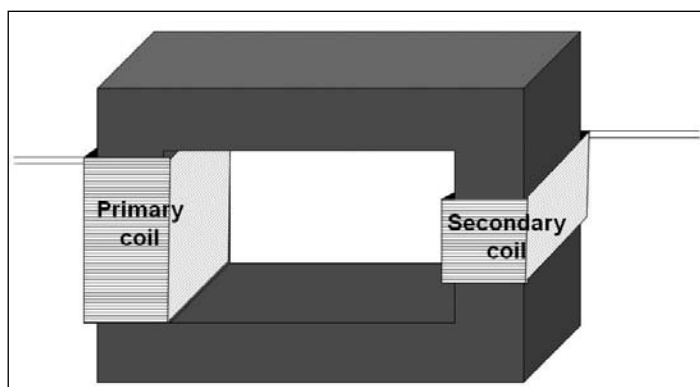


Figure 9. A transformer is two coils of wire - the primary and secondary coils - wrapped around a piece of iron. It makes AC voltages larger or smaller. A transformer with more turns in the primary coil (as below) decreases the voltage and is a step-down transformer. The reverse arrangement produces a step-up transformer which increases the voltage (but proportionately decreases the current)

CAPACITANCE, INDUCTANCE AND IMPEDANCE

Capacitance

Capacitance describes the ability of an object to store electrical charge and is measured in *farads*. Capacitors store electrical energy and generally consist of a pair of metal plates, separated by a non-conductor (the *dielectric*). They have a potential difference between them but cannot conduct direct current continuously, because of the presence of the non-conductor. When exposed to a direct current, the plates store charge (and current transiently flows) until the voltage between the plates equals that of the supply voltage; the capacitor is now charged.

Capacitors can conduct AC current since the plates alternately charge and discharge as the direction of current flow changes (Figure 10).

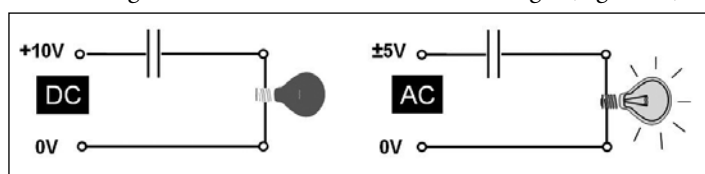


Figure 10. Capacitors prevent the flow of direct current (after an initial current flow which charges the capacitor to the applied voltage). Alternating current is conducted to an extent that depends on the capacitance of the capacitor and the frequency of the AC current

The energy stored by the capacitor is calculated by, $E = \frac{1}{2}C \times V^2$.

Capacitance exists between many objects in theatre which act as pairs of plates (e.g. between the ECG leads, the patient, a theatre light and the table), with the air acting as the insulator between them. This *capacitive coupling* can cause electrostatic interference; an example is the interference from diathermy as a result of capacitive coupling between an insulated diathermy lead, overlying an ECG lead. Allowing current flow between the terminals of a charged capacitor discharges it and releases the stored energy.

Inductance

Inductance arises in circuits with alternating or oscillating currents. As the current reverses, the associated magnetic field (see above) in a coil or loop of wire waxes and wanes. The fluctuating magnetic field *induces* a current in the same wire in the opposite direction to original current, which is in opposition to the original change (*Lenz's Law*).

Inductance is proportional to rate of change of current (i.e. the AC frequency) and the number of turns in the coil. Hence the resistance to current flow (the impedance – see below) is *frequency dependent*.

Impedance

This is a fundamental concept in AC circuits and signal processing, describing the opposition to the passage of current. Impedance is analogous to resistance in DC circuits and, like resistance, is measured in *ohms*. Impedance is given the symbol, *Z*.

The magnitude of impedance depends upon a complex relationship between the signal frequency and the capacitance, inductance and resistance of circuit. It is the *frequency dependence* of impedance that makes it possible to build circuits which present high impedance to one range of frequencies and low impedance to others - this is the basis of *electronic filters*.

Electronic filters

Filters act to create a low impedance path to transmit signals in a desired frequency range (e.g. the ECG signal) while attenuating all other frequencies. They are described by their transmission characteristics:

- *High pass* - transmit frequencies *above* a cut-off frequency,
- *Low pass* - transmit frequencies *below* a cut-off frequency,
- *Band pass* - transmit frequencies within a middle range (a band).

CLINICAL ROLE OF CAPACITORS AND INDUCTORS

Defibrillators

Defibrillation is the application of a preset electrical current across the myocardium to cause synchronous depolarization of the cardiac muscle, with the aim of converting a dysrhythmia into normal sinus rhythm.

The most important component of a defibrillator is a capacitor (Figure 11), which stores a large amount of energy in the form of electrical charge, then releases it over a short period of time. For successful defibrillation, the current delivered must be maintained for several milliseconds. The current and charge delivered by a discharging capacitor decay rapidly and exponentially. Inductors therefore have a role in prolonging the duration of current flow.

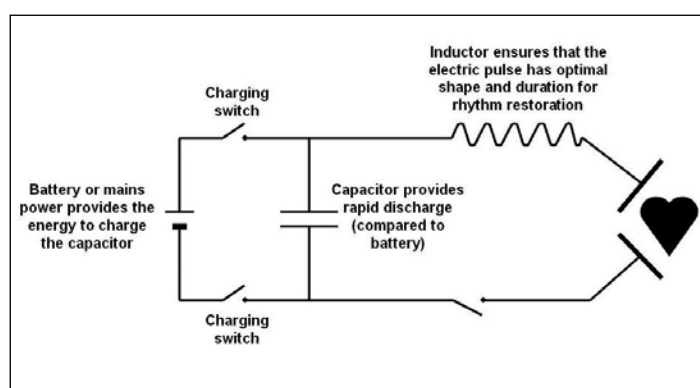


Figure 11. Schematic diagram of a defibrillator. The charging voltage is approximately 5000V and the total current delivered is up to 35A. The stored energy of the capacitor is $\frac{1}{2}C \times V^2$

Monophasic and biphasic defibrillators (Figure 12)

In many countries biphasic defibrillators have replaced monophasic defibrillators. They require lower energy levels to achieve defibrillation and the risk of damage to the cardiac muscle is therefore less. Smaller capacitors are required and batteries have longer life.

AMPLIFIERS

Principles

An amplifier increases the *power* of an electrical signal – the output signal is *proportional to input but of greater magnitude*. The ratio between output and input is the amplification factor or gain, with the power gain expressed in decibels (dB). Voltage gain is the ratio of input signal voltage to output voltage.

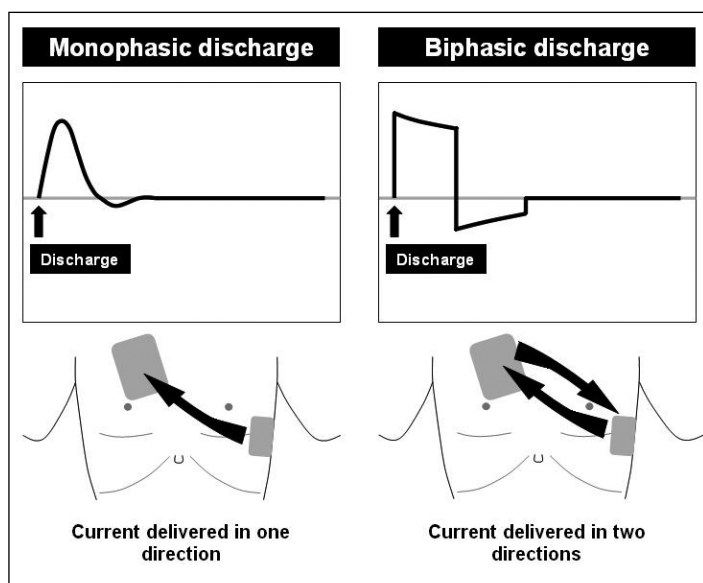


Figure 12. Biphasic defibrillators – the current waveform is electronically regulated

An ideal amplifier should have the following properties:

- a good *signal to noise ratio* (expressed in dB),
- a *linear frequency response* over its working frequency range (Figure 13),
- an output signal which does not drift with time or temperature (Figure 14)- achieved with careful design, re-zeroing and thermal compensation,
- minimal *hysteresis* within the system (Figure 15),
- an adequate *dynamic response* over its working frequency range. Gain should be constant for all frequencies in the signal and any phase change or delay should be the same for all frequencies in the signal, i.e. optimal damping (see *Biological signals article*).

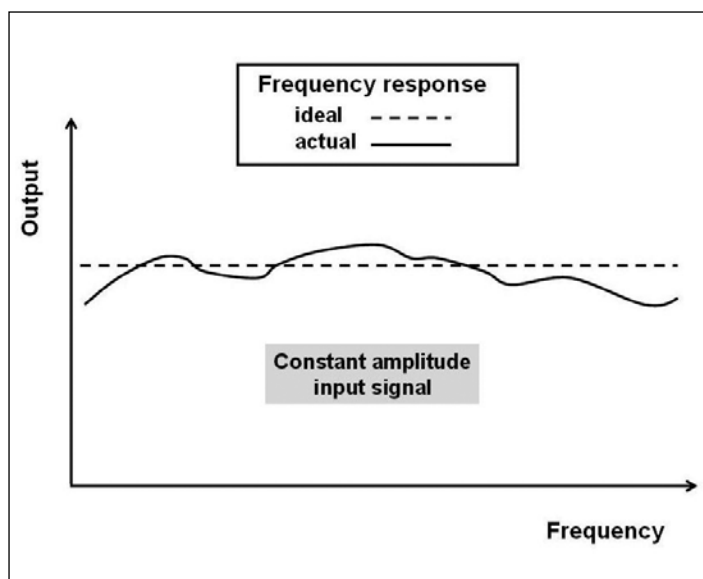


Figure 13. A non-linear frequency response is shown

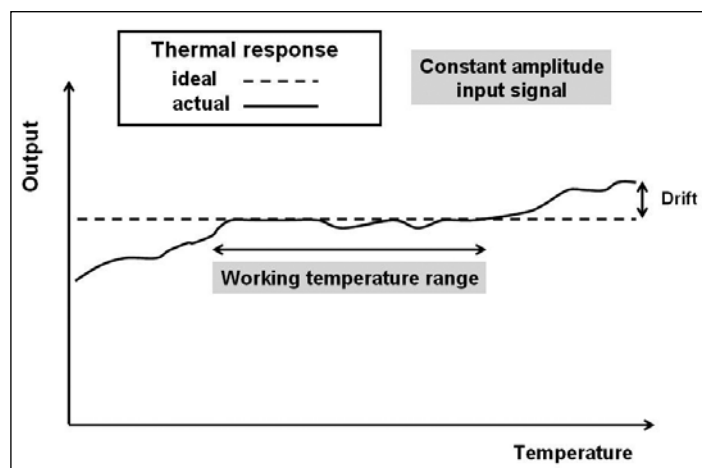


Figure 14. Example of an amplifier with thermal drift

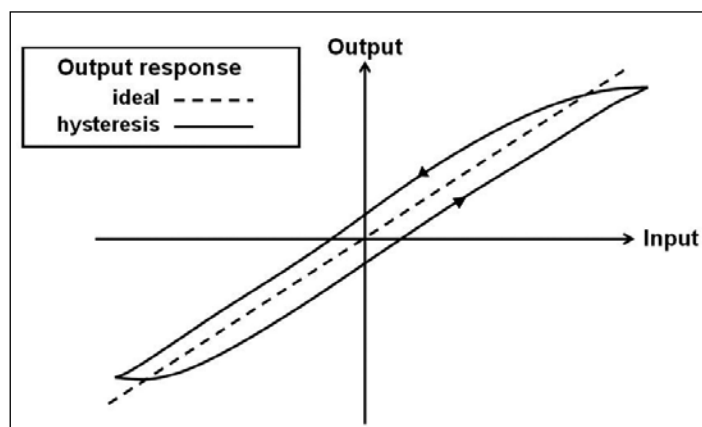


Figure 15. Hysteresis – for a certain input the output is different, depending on whether the input is increasing or decreasing

Differential amplifiers

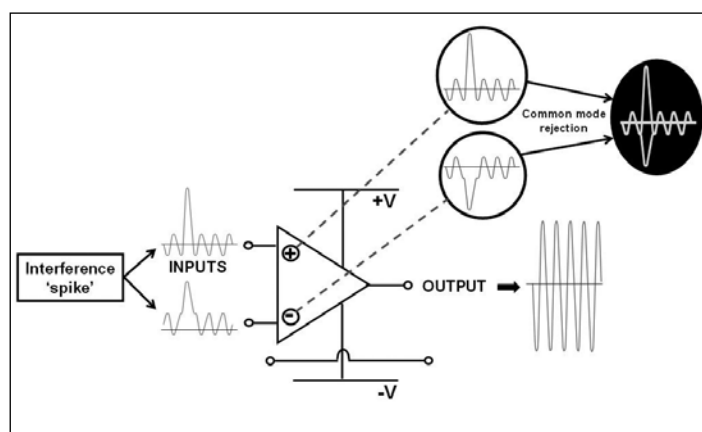


Figure 16. A differential amplifier uses a 'common mode rejection' to exclude interference common to two separate inputs, thereby improving the 'signal to noise ratio' of the remaining signal

Amplifiers in clinical practice

- Amplification of biological signals is usually performed in several stages. Maximum transfer of signal power occurs when output and input impedances are equal (*impedance matching*).

- Negative feedback is used to stabilize amplifiers and prevent oscillations.
- The frequency response can be modified to enhance amplification of a relevant frequency band (*active filter*).
- Differential input amplifiers are generally used in biomedical equipment and they provide considerable improvement in *signal to noise ratio*.

SOURCES OF INTERFERENCE

Noise

This is interference superimposed on the required signal. It may be extraneous or introduced within monitoring equipment. Any interference reduces the *signal to noise ratio* and degrades the quality of the information available.

Interference sources include:

- Electrostatic induction - electrical potentials induced in the patient by adjacent electrical fields,
- Electromagnetic induction,
- Electrode contact potentials (Ag-AgCl),
- Movement artifacts - skin potentials and induction,
- 50Hz mains and switching spikes,
- Radiofrequency energy - broadcast (mobile phones) and diathermy - high frequency and high power.

EFFECTS OF ELECTRICITY ON THE BODY

Electrocution means to kill by electricity. The effects of electricity passing through the body depend upon current density and the path taken. High current densities deliver large amounts of energy and cause burns. Low current densities can still be dangerous because of their effects on excitable tissues, notably the heart. The response to different current levels varies between individuals.

Table 1. Macroshock - the effects of a hand to hand AC current at 50Hz for 1 second

Current	Effect
(< 1mA	No sensation - microshock)
1mA	Tingle
5mA	Pain
15mA	No-let-go threshold - tetanic contraction
50mA	Respiratory arrest - respiratory muscles in tetany
75mA	Arrhythmias, ventricular ectopics and myocardial 'pump failure'
100mA	VF cardiac arrest
> 5A	Asystole

There are two main risks:

1. **Macroshock.** The current flow is greater than 1mA and is sensed by the individual.
2. **Microshock.** The current is 100mcA to 1mA, is too small to be sensed but can be hazardous if a part of the equipment is applied to the heart (e.g. central venous lines).

Microshock

The intracardiac VF threshold is 60-100mcA with a small surface area electrode. Below the sensory threshold, the shock cannot be felt and this is termed microshock. Intact dry skin is the most important safeguard against shocks. Lowering the skin resistance with contact electrodes or saline substantially increases the current for any given applied voltage.

DIATHERMY

Definition

The generation of heat in body tissues by passage of a high-frequency electric current between two electrodes, placed in or on the body. When applied specifically to surgery the high-frequency current, at the tip of a diathermy knife, produces sufficient heat to cut tissues, or to coagulate and kill cells, with a minimum of bleeding.

Principles

A voltage source from an electrosurgical generator is applied across the tissue causing an electrical current to flow. This forms a simple electrical circuit, with the tissue acting as a resistor. Current flowing through the resistance of the tissue causes the generation of heat within the tissue itself, and the heat causes the tissue damage. The resistance of the tissue converts the electrical energy of the voltage source into heat (thermal energy), which causes the tissue temperature to rise:

$$\text{Heat produced} = \text{Electrical energy expended}$$

Excitable tissues are very sensitive to low frequency alternating current and stimulation ceases above about 100kHz, therefore diathermy uses a range between 200kHz to 5MHz. In this frequency range electrosurgical energy causes minimal neuromuscular stimulation and no risk of electrocution.

Diathermy circuits are either *bipolar* or *monopolar*, and different effects on tissues are achieved by varying the electrical waveform and/or the power level.

Bipolar diathermy

The active and return electrode functions are both accomplished *at the surgical site*, with the current path confined to tissue grasped between the tips of the forceps. Current does not spread through the patient's body.

Monopolar diathermy

The active electrode is in the wound and the patient return electrode is attached somewhere else on the body. The current flows through the patient to the patient return electrode and then back to the generator. Monopolar diathermy is versatile and clinically effective.

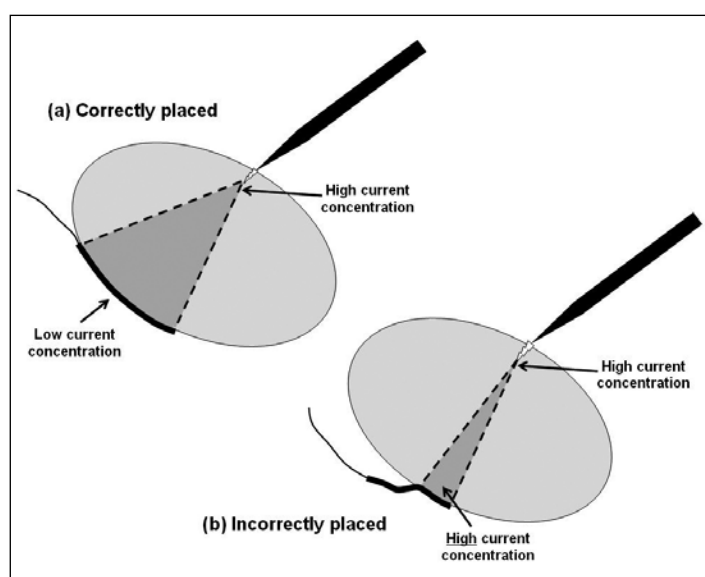


Figure 17. If the return electrode of monopolar diathermy is poorly placed (b) there is increased current density and a risk of burns. Modern generators monitor the adequacy of contact by measuring the impedance between the pad and patient. There is an inverse relationship between impedance and contact area and, if it detects a dangerously high level of impedance at the patient/pad interface, the system deactivates the generator before injury can occur

Modern generators have *isolated circuits*, which eliminate many hazards inherent in earthed systems. If the return electrode circuit to the patient is broken, an isolated generator will deactivate the system because the current cannot return to its source. The function of the patient return electrode is to remove current from the patient safely. It carries the same current as active electrode but the effect of the current is less because of its size and relative conductivity; the *current density is lower*. The more concentrated the energy, the greater the thermodynamic effect.

The extent of the burn is governed by the relationship:

$$\text{Burn} = \frac{\text{current} \times \text{time}}{\text{area}}$$

Other risks of diathermy:

- A potential source of ignition risking fires or explosions.
- *Direct coupling of current* - the user accidentally activates the generator while the active electrode is near another metal instrument. The secondary instrument will then become energised.

Table 2. Classes of secondary protection

Class I	All exposed electrically conductive parts are connected to earth potential by a conductor which will convey any leakage current to earth.
Class II	No protective earth. Basic insulation is supplemented by a second layer of insulation (double insulated). No exposed conductive parts can contact the live conductors.
Class III	Protection relies on supply of power at safety extra low voltage (SELV) - 24V (Root mean square).

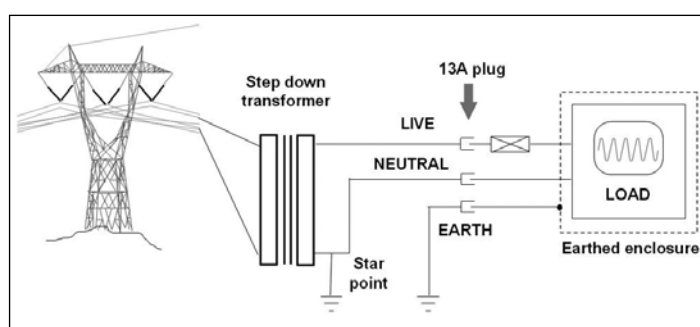


Figure 18. Distribution of 240V mains electricity

- *Capacitive coupled current* - an 'inadvertent capacitor' may be created by the surgical instruments. The conductive active electrode is surrounded by nonconductive insulation. If this, in turn, is surrounded by a conductive metal cannula, the current in one conductor can, through the electrostatic field, induce a current in the second conductor.

OTHER ELECTRICAL HAZARDS

Mains electricity

Hazards mainly arise from mains powered equipment.

Primary protection from hazards

Insulation

Basic protection against electric shock from mains powered equipment is provided by insulation. All 'live' parts in equipment are separated from each other by non-conducting material. If damaged, a live component may 'short' to the case raising it to mains voltage, constituting a single fault condition. Medical equipment must remain safe under single fault conditions and so *secondary protection* is required.

Secondary protection from hazards

There are three classes of secondary protection (Table 2):

Equipment should only become hazardous if two faults are present simultaneously, for example a short to the case *and* a broken earth lead. The result of a 'two fault' state such as this would be a *live enclosure* - if touched current will flow to earth through the patient or a staff member. This is prevented by regular servicing and testing for both types of fault separately, aiming to detect a single fault condition before the second fault occurs.

Prevention of microshock

Microshock is hazardous when there is a low impedance piece

of equipment placed in contact with the patient. An example is an intracardiac catheter (central line), which should contain 5% glucose, not an ionic (and therefore conductive) solution such as 0.9% saline.

Stringent criteria are set for the maximum permitted leakage current from equipment placed in contact with a patient and this depends on the nature of that contact. Three groups of equipment are considered suitable for direct connection to patient - these are coded B, BF and CF. 'F' denotes that the part applied to the patient is isolated from all other parts of the equipment, i.e. it is 'floating'. The maximum leakage current (British standard, BS 5724) for each class of equipment is shown in Table 3.

Table 3. Maximum leakage standards for different classes of equipment

BS 5724 standards	BF	CF
Earth leakage	500 (1000)	500 (1000)
Enclosure circuit	100 (500)	10 (500)
Patient circuit	100 (500)	10 (50)

All currents are in microamps (mcA).

(Bracketed figures) denote permitted leakage current in a single fault condition.

Type BF - can only be applied to body surface.

CF - the category for equipment with potential direct cardiac connection.

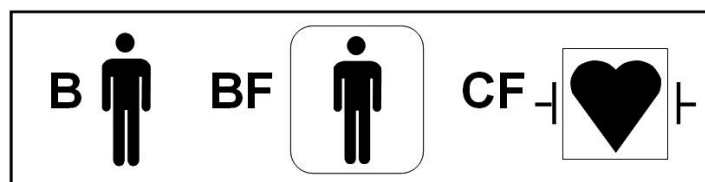


Figure 19. Labels identifying classes of equipment used in contact with patients

Other methods of protection

Maintenance

Programs of regular maintenance are essential to detect and correct faults.

Isolation

The major means of protection is isolation of the applied part, meaning that the input circuitry is electrically isolated from the other components of the equipment. Isolation is achieved through:

- Earth leakage contact breakers. These are not sensitive enough to detect microcurrents and may be too slow to guarantee protection.
- Isolation transformers provide an *earth-free mains* connection.
- Opto-isolation is used in most electronic equipment. An optical isolator is a device that uses a short optical transmission path to transfer a signal between elements of a circuit.

Practical considerations for theatre

- No long cables,
- No distribution blocks,
- Pendant (hanging) electrical supplies,
- Beware of and change chaffed cables,
- Keep the patient's skin dry,
- Check maintenance reports regularly,
- Use earth leakage circuit breakers.

CONCLUSION

Electricity is now available in most theatres around the world and many of the technologies available for patient care, monitoring and safety rely upon it. Whilst many anaesthetists will not seek a detailed understanding of the circuitry within their equipment, some basic knowledge is essential to minimise any risks of harm to the patient by inadvertent exposure to electrical current. This is particularly important where the facilities for regular servicing are stretched or unavailable, when the ability to keep equipment safe and functional is the responsibility of the anaesthetist.

Heat Production and Loss

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DEFINITIONS

Heat:	Heat is a form of energy that can be transferred from one (a hotter) object to another (a colder) object, the energy being in the form of the kinetic energy of the molecules of the object.
Temperature:	Temperature is the thermal state of an object which determines whether it will give heat to another object or receive heat from it. Heat is transferred from the object at the higher temperature to the object at the lower temperature.
Calorie:	The SI (Système International d'Unités) unit of heat is the same as that of energy, namely the Joule (J). The calorie is used here where 1 calorie = 4.186 J. Calorie spelt with a capital 'C' represents 1000 calories when it is used in dietary nutrition.
Celsius/centigrade:	The temperature scale is the Celsius (°C) (after Anders Celsius), or centigrade scale, because under standard conditions water freezes at 0°C and boils at 100°C.
Conduction:	Conduction is heat transfer through a solid medium. Conduction is the process whereby heat energy is transmitted through a substance by the transfer of the energy of motion of the molecules to adjacent molecules. Metals are good conductors of heat but gases are poor conductors. The air surrounding a person provides protection from heat loss through conduction.
Convection:	Convection is the heat transfer through a fluid medium such as air or water. This occurs because the warmer molecules move within the fluid, i.e. float to the top when warm or sink to the bottom when cool. The air layer next to the surface of the body is warmed by conduction and as it is heated it expands, becomes less dense and so rises. The resulting convection current carries heat away from the body.
Radiation:	All objects absorb, reflect or emit electromagnetic energy (radiation) over a spectrum of wavelengths. Such energy includes light waves and heat as infrared waves. The radiation emitted carries energy away from the object and causes it to cool down. If this energy is absorbed by another object, that object will become hotter. Thus radiation can transfer heat energy between two objects which are not in contact.
Latent heat of vaporization:	The amount of heat required to increase the energy of a fluid to change its state from liquid to vapour without any temperature change is called the latent heat of vaporisation.
Evaporation:	Evaporative heat loss is due to the loss of latent heat of vaporisation of moisture or other solutions applied to the skin's surface. The loss of heat by this route is dependent on the total area of skin exposed to the atmosphere.
Critical temperature:	Neutral temperature is the ambient temperature that results in minimal oxygen consumption. Critical temperature is the ambient temperature below which an unclothed, unanesthetised individual cannot maintain a normal core temperature. The lower limit of the thermoregulatory range (critical temperature) is 1°C for an adult, but is 23°C for the full term infant and 28°C for the premature infant. The thermoregulatory range of the neonate is narrower than that of the adult and the operating rooms must be kept at least 23°C for neonates. Note that the thermoregulatory zone is different to the thermoneutral zone – the temperatures between which we do not have to actively regulate our body temperature.

Summary

Under general anesthesia the body cannot compensate for hypothermia because anesthetics inhibit central thermoregulation by interfering with hypothalamic function.

Anesthetic-induced vasodilatation causes redistribution of heat from the warm central compartment to cooler peripheral tissues.

Even mild core hypothermia can be detrimental and lead to patient harm. It is therefore important to monitor core temperature during general anesthesia and take active measures to conserve heat. Induced hypothermia has proved to be protective during times of cerebral or cardiac ischemia as metabolic oxygen requirement is lowered by systemic cooling. Hyperthermia during sepsis, hyperthyroidism, malignant hyperthermia, and drug or transfusion reactions if not recognized and treated promptly can lead to life-threatening physiological disturbances.

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HEAT PRODUCTION AND LOSS

Humans are homeothermic as they actively maintain their core body temperature within a narrow range, usually 36.5-37.3°C. When core body temperature changes outside this range of 0.5-0.8°C, various

thermoregulatory mechanisms are activated to bring the temperature back to normal. Anesthesia disrupts many aspects of thermoregulation, leading to perioperative hypothermia, which in turn can lead to several complications. Often, measurement of temperature is

Table 1. Neutral and critical temperatures

	Neutral Temperature °C	Critical Temperature °C
Preterm neonate	34	28
Term neonate	32	23
Adult	28	1

neglected during and after anaesthesia. By understanding the physiology of thermoregulation and the impact of anaesthesia on this process, one can use simple steps to maintain normal body temperature in the perioperative period and thereby prevent adverse patient outcomes.

PHYSIOLOGY

The brain uses negative feedback mechanisms to maintain body temperature within a narrow range, which ensures that chemical reactions at a cellular level can occur optimally. Body temperature increases with metabolic activity – it is lowest during sleep, higher during the day, with oral temperatures between 36.5 and 37.3°C in the morning in normal adults. In menstruating women, body temperature can increase up to 1°C at ovulation due to the effect of luteinizing hormones.

In order to understand the impact of anaesthetics on the process of thermoregulation and how different parts of the body have different temperatures, it is useful to construct a two-compartment model of the human body. Imagine that the body is divided into a central core compartment surrounded by a peripheral compartment (Figure 1). The core is made up by major thoracic and abdominal organs and the brain, holds two-thirds of the body heat content, and is maintained within a narrow temperature range (36.6 to 37.4°C). The periphery is by the limbs and skin and subcutaneous tissue, and contains about one-third of the body heat content. The temperature of the periphery varies widely from 0°C up to 40°C depending on the environment, but is usually 30–32°C. This 5–7°C difference between core and peripheral body temperature is maintained by vasoconstriction in the blood vessels leading to the peripheral tissues.

Heat production

Heat is produced as a by-product of normal metabolic activity. In a body at rest, the basal metabolic rate (BMR) is about 40kcal.m⁻².h⁻¹, which is about 1700kcal.day⁻¹ in an adult man weighing 70 kg. Roughly two-thirds of the energy available from the metabolism of glucose, amino acids, or fat is dispersed as heat; the rest is stored as chemical energy in the form of ATP (adenosine triphosphate). Metabolism of fat releases almost twice the energy (9.3cal.g⁻¹) when compared to that of glucose and amino acids (4.1cal.g⁻¹).

Heat production can be increased by voluntary muscle activity (exercise), involuntary muscle activity (shivering), or non-shivering thermogenesis. Heat production can be increased up to six-fold while shivering, and up to 20-fold at maximum intensity of exercise.

In brown adipose tissue, when all the energy of metabolism is dispersed as heat without storing any in ATP, it is called non-shivering thermogenesis. In neonates without significant muscle mass, non-shivering thermogenesis is an important method of heat production.

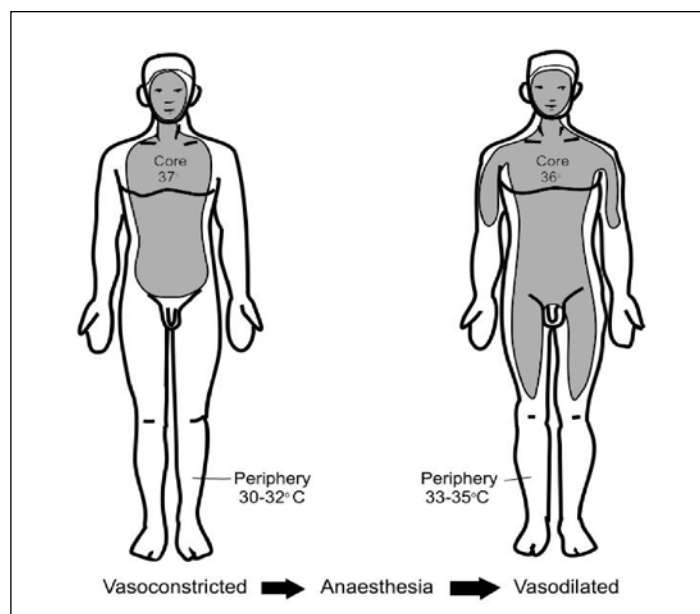


Figure 1. The effects of anaesthesia on heat balance. The human body consists of two compartments in this model. At baseline, the central core is considerably warmer than the periphery. By inhibiting tonic vasoconstriction, both general and regional anaesthesia decrease core temperature by redistribution of heat from the central core to the peripheral thermal compartment. This mechanism explains the decrease in core temperature of 1°C in the first 30–60 minutes following induction of anaesthesia. As the periphery is now warmer, further heat loss occurs as the gradient between the skin and surroundings is greater

(Modified with permission from Doherty M and Buggy D. Thermoregulation. In: Hemmings & Hopkins, ed. Foundations of Anaesthesia, 2nd Edition, Philadelphia: Elsevier; 2006: 809–826)

Brown adipose tissue has an abundant vascular supply and sympathetic innervation. Non-shivering thermogenesis is inhibited by sympathetic blockade and by inhalational agents.

Metabolic rate is higher in children, and metabolic activity is increased by hormones such as thyroxine and growth hormone. Under normal conditions, body heat is preserved by tonic peripheral vasoconstriction.

Heat loss

Heat loss occurs by conduction, convection, and radiation of heat from the body to the surrounding area, and by evaporation of sweat.

Heat loss by conduction occurs by direct contact of the body with an object of lower temperature and contributes to only 1–2% of heat loss.

A layer of air normally trapped next to the skin contributes to insulation. Clothing increases this insulating layer and prevents heat loss to the environment. Convective heat loss occurs when the layer of air next to the skin moves and carries heat away from the body. In an operating room with forced airflow, convection can account for 25% of the heat loss or more. The amount of heat lost by convection depends on the surface area of the body that is exposed and the amount of airflow. As a reminder, at the same temperature, windy days feel cooler than calm days.

Heat loss by evaporation is increased in the operating room from the evaporation of skin-preparation solutions and in major surgeries with open abdominal cavities. Evaporative heat loss is more significant in premature neonates because of their increased skin permeability.

Radiation is transfer of heat by infrared waves from the body to cooler objects (not in physical contact with the body) in the surrounding area, and constitutes the major method of heat loss to the environment. Almost 60% of heat loss can occur via radiation. The amount of heat loss depends on the fourth power of the temperature difference between the objects. If the operating room temperature is decreased by 2°C, heat loss will be increased by a factor of 16 (2⁴).

Normal respiration accounts for a small amount of the total heat loss, typically 10%. Eight per cent of this loss occurs through increasing the humidity of the inspired air to 100%, and 2% is due to warming the air. Under anesthesia the inspired gases are usually dry and heat is lost in both humidifying the air and in warming dry air. Heat loss through this route can be avoided by humidifying inspired gases and is reduced when low fresh gas flows are used in an anesthetic circle system with soda lime, instead of high flows through a non rebreathing system. Loss of heat through this route becomes important when high fresh gas flows are used, especially in small children.

A patient under anesthesia in an operating room loses or gains body heat via some combination of conduction, convection, radiation, or evaporation. The major mechanism of heat loss or gain varies with time and depends upon the phase of the anesthetic, set temperature and humidity of the operating room, air-conditioning and net air-flow or air-exchange in the operating room, whether or not the patient is draped with impervious (plastic or paper) drapes or pervious (linen) drapes, the total surface area of the body exposed and whether or not major body cavities (thorax or abdomen) are open and institution of active methods of patient cooling or warming.

Physiological Control

The main site of thermoregulation is the hypothalamus, which receives information from temperature sensitive nerve endings throughout the body. The sense organs for temperature are the unsheathed nerve endings in the skin and subcutaneous tissue that respond to temperatures above or below core temperature by changing the rate at which they send impulses to the central nervous system. Cold receptors – neurones that respond to temperatures from 10 to 36°C – are present in a large number in the peripheral compartment when compared to warm receptors that respond to 30 to 45°C. The sensation of heat or cold produced by a temperature change gradually fades because the neurons are subject to adaptation between 20 and 40°C. The skin provides about 20% of the total thermal input to the central nervous system, while thermally sensitive cells throughout the body provide the rest of the input. The input from various sites is integrated in the anterior hypothalamus.

The posterior hypothalamus compares the aggregate thermal input with the set point temperature and initiates appropriate responses when necessary. The temperature at which a response is triggered is termed the threshold temperature. The threshold temperature may change with gender, exercise, food intake, and during infection, and may be altered with certain drugs. The threshold for vasoconstriction

is 36.5°C and 36.0°C for shivering. General anesthesia lowers this threshold by 2-3°C. The inter-threshold range is the range of core temperatures at which no thermoregulatory response is triggered. This range is normally 0.2-0.5°C, but general anesthesia can increase this range to 5.0°C (Figure 2).

Changes in temperature beyond the inter-threshold range initiate efferent responses that increase heat production (shivering or non-shivering thermogenesis), or decrease heat loss (vasoconstriction) in response to cold; or increase heat loss (sweating and vasodilatation) in response to warmth. When core temperature decreases, initially muscle tone is increased, and then shivering occurs. Shivering is an involuntary skeletal muscle activity that occurs once the cold core temperature threshold is reached (36.0°C). Sustained shivering can double heat production. Shivering after anesthesia is distressing for the patient and can increase pain by involuntary movement of muscles splinting the surgical site. Even though oxygen consumption is increased by shivering, it does not cause hypoxemia. In fact, hypoxemia inhibits shivering. Pethidine, in a dose of 0.3mg.kg⁻¹ IV, stops postanesthetic shivering. However, the patient must be actively warmed to raise core temperature and treat this hypothermia, or to prevent hypothermia from occurring in the first place.

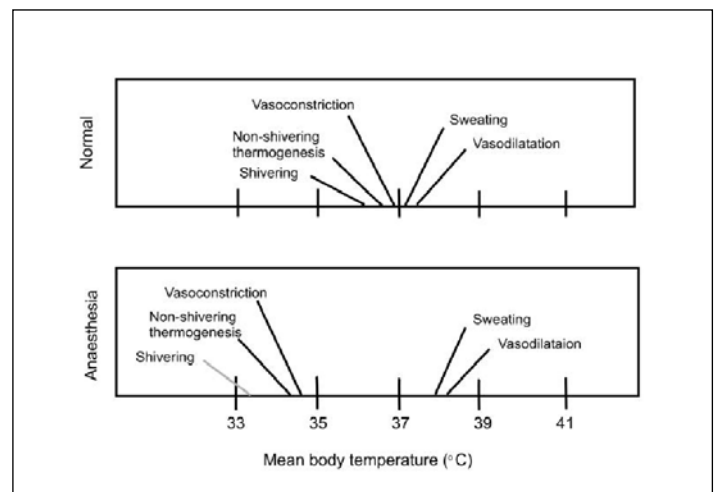


Figure 2. Threshold temperature for initiation of thermoregulatory effector responses. For each response the threshold is indicated by the intersection with the x-axis. (A) Normal: note the temperature range within which no autonomic effector is activated is about 0.5°C; (B) Anaesthesia: the threshold temperature for activation of cold responses (vasoconstriction and shivering) is shifted to the left, and for warm responses (vasodilation and sweating) is shifted to the right. The temperature range within which no thermoregulatory effector is activated is increased up to 5°C

(Modified with permission from Doherty M and Buggy D. Thermoregulation. In: Hemmings & Hopkins, ed. Foundations of Anesthesia, 2nd Edition, Philadelphia: Elsevier; 2006: 809-826)

MEASUREMENT OF TEMPERATURE

Body temperature can be measured at various sites, including the skin at the axilla (over the axillary artery), tympanic membrane, oral cavity, nasopharynx, distal esophagus, rectum, or urinary bladder and in the pulmonary artery. Core temperature can be measured in the nasopharynx or lower esophagus. An oesophageal stethoscope with

a thermistor positioned to hear both the heart sounds and breath sounds is ideal. Rectal and bladder temperatures can be erroneous as measures of core temperature since those organs are not sufficiently well-perfused to reflect changes in core heat content. Recently temporal artery thermometers have become available to measure temperature over the forehead. These may be more consistent when compared to devices that measure tympanic membrane temperatures as measured through the external auditory canal.

EFFECTS OF ANESTHESIA

General anesthesia typically leads to core hypothermia which occurs in three phases. In the first hour following induction of anesthesia, there is a rapid reduction of 1.0-1.5°C in the core temperature due to redistribution of heat from the core to the periphery because of anesthetic-induced vasodilatation. As basal metabolic rate is reduced by 20-40% during anesthesia, heat loss could exceed heat production in the next 2-3 hours and lead to continued gradual reduction in core temperature. In the third phase when patients become sufficiently hypothermic and vasoconstriction occurs at the lower temperature threshold, heat loss and heat production are matched. This is the plateau phase. The pattern of hypothermia during spinal or epidural anesthesia is similar to that of general anesthesia for the first two phases. As vasoconstriction is blocked due to the regional anesthetic, the plateau phase may not occur and serious hypothermia could occur (Figure 3).

CONSEQUENCES OF HYPOTHERMIA

Hypothermia has adverse effects on patient outcome, including an increased incidence of myocardial ischemia and cardiac morbidity,

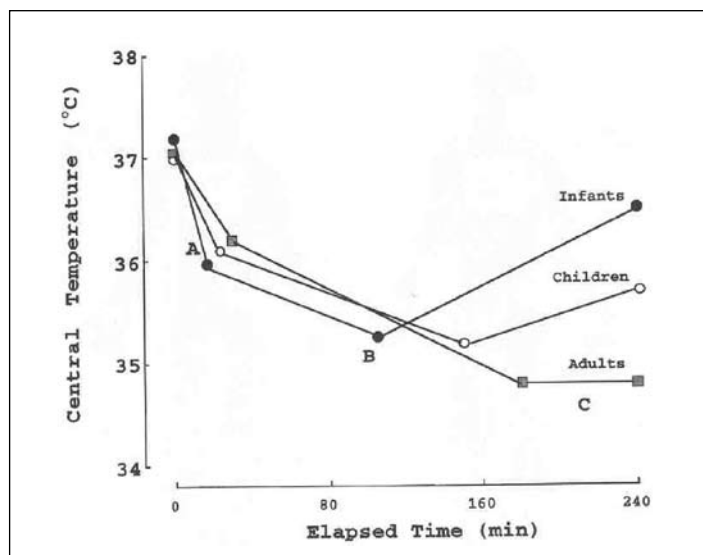


Figure 3. This represents the typical pattern of heat loss during anesthesia, which occurs in three phases for infants (closed circles), children (open circles), and adults (squares). (A) Redistribution of heat from the core to the periphery following induction of anesthesia; (B) Heat loss to the environment; (C) Steady state and rewarming

(Modified with permission from Bissonnette & Ryan. Temperature Regulation. In: Cote, Todres, Goudsouzian, Ryan, eds. A Practice of Anesthesia for Infants and Children, 3rd Edition, Philadelphia: Elsevier; 2001: 610-636).

arrhythmias, interference with coagulation, increased blood loss, and postoperative shivering. Mild hypothermia has an increased risk of postoperative sepsis, surgical wound infection, prolonged postanesthetic recovery, and prolonged hospitalization.

In patients with core hypothermia with a temperature of 34.5-35.9°C, increased plasma catecholamine concentrations lead to hypertension, myocardial irritability, and can induce myocardial ischemia and arrhythmias. Inadequate hemostasis due to impaired platelet function, and suboptimal clotting factor activation as a result of hypothermia can lead to increased blood loss and increased blood transfusion requirement.

Hypothermia can induce vasoconstriction in the skin and subcutaneous tissues leading to a lower tissue oxygen tension, setting up conditions for poor wound healing and wound infection. Mild hypothermia directly impairs immune function, including B cell-mediated antibody production and nonspecific oxidative bacterial killing by neutrophils.

Hypothermia slows drug metabolism. The duration of action of vecuronium is more than doubled in patients with a core temperature less than 35°C. Solubility of inhaled anesthetic agents increases in hypothermia with a decrease in MAC of 5% for every one degree decrease in core temperature. Hypothermia increases plasma concentrations of propofol by thirty percent with a three degree decrease, and fentanyl by five per cent per one degree decrease in core temperature. This can lead to delayed awakening from anesthesia in patients who are hypothermic, thereby increasing the length of their stay in the recovery room.

PREVENTION AND TREATMENT OF HYPOTHERMIA

Remember that prior to surgery patients are unclothed and relatively less insulated. They maintain their core temperature by active peripheral vasoconstriction. Induction of anesthesia causes general vasodilatation and transfers heat from the core to the periphery, unmasking this heat deficit. By actively warming the peripheral tissue in the preoperative period by exposing the patient to radiant heat or using a forced-air convective warmer over one hour, the peripheral compartment can be warmed and the transfer of heat from core to

Consequences of hypothermia

1. Shivering in the recovery room
2. Cardiac morbidity
3. Poor wound healing
 - a. Reduced tissue oxygen tension
 - b. Immunosuppression
4. Delayed emergence due to slowing of drug metabolism
 - a. Prolongation of neuromuscular blockade
 - b. Delayed emergence
 - i. Prolonged elimination of inhaled agents
 - ii. Increased plasma concentration of propofol and fentanyl

periphery that occurs upon induction of anesthesia can be avoided. However, rapid warming can lead to sweating.

Insulating the patient using one layer of an insulator (linen blanket) reduces heat loss by 30%, as it traps a layer of air between it and the skin; however, more passive insulation (additional blankets) is of little benefit. Once heat has been distributed from the central core to the periphery after induction of anesthesia, the core may be rewarmed by actively rewarming the periphery and creating a peripheral to core heat transfer. An electrically powered air heater and fan can be used to warm the patient's peripheral compartment by blowing warm air into a disposable patient cover placed directly over the patient's skin. The amount of heat transferred depends on the extent of body surface covered using these covers. It is crucial to remember not to rewarm ischemic tissues until blood flow is first restored (any limb under a tourniquet).

Intravenous fluid at room temperature can reduce core temperature unless actively warmed. One liter of IV fluid can reduce core temperature by approximately 0.25°C. One unit of refrigerated red blood cells at 4°C can reduce core temperature by 0.25°C. Fluid warming is, therefore, essential when large amounts of fluid are to be administered. Active fluid warming will prevent hypothermia

Prevention and treatment of hypothermia

1. *Preoperative period*
 - a. Warm environment with ambient temperature above the critical temperature
 - b. Insulated patient with at least one layer of insulation
2. *Intraoperative period*
 - a. Warm Operating Room
 - b. Insulated patient
 - c. Forced air warming as soon as possible
 - d. Circulating water mattress under the patient when feasible
 - e. Heating lamps in neonates
 - f. Warmed IV fluids when large volume of fluids are used
 - g. Warmed blood using in line warmers
 - h. Cardiopulmonary bypass warming
 - i. Field irrigation with warmed fluids
 - i. Wound wash outs with large volumes of fluids
 - ii. Peritoneal or pleural cavity irrigation
 - iii. Bladder irrigation cystoscopy
3. *Postoperative period*
 - a. Forced air warming
 - b. Circulating water mattress in the ICU
 - c. Pethidine (0.3 mg.kg⁻¹ intravenous or intramuscular) for active shivering.

but not actually warm the patient unless large amounts of blood are transfused rapidly.

As less than 10% of metabolic heat loss occurs via the respiratory tract, airway humidification contributes very little to actively warming the patient.

SPECIAL CONSIDERATIONS

Neonates and infants

Infants, especially neonates and preterm babies, are at very high risk for perioperative hypothermia. This is because of their increased surface area to volume ratio, thin skin with minimal insulating fat, and less effective efferent responses to cold temperatures. Infants under the age of 3 months cannot shiver. Non-shivering thermogenesis, the major mechanism of heat production, increases the metabolic rate and oxygen consumption and may strain the cardiopulmonary system, especially in a sick child, or one with cyanotic congenital heart disease. The critical temperature, the temperature at which an unclothed infant does not lose heat to the environment, is higher in infants than in adults. The ambient temperature must be raised to 24°C or above, and the infant should be wrapped and transported in an incubator. At induction and during emergence, infants should be placed on a heating blanket or under an overhead radiant heater. During surgery, use of forced air heating, warmed IV fluids, and warmed humidified gases will decrease heat loss.

Cardiopulmonary bypass

During cardiac surgery, mild deliberate hypothermia to 34°C is used for myocardial, cerebral, and spinal cord protection. Brain metabolism is reduced by 50% at 28°C. Recently, patients are also being cooled actively for 24 to 48 hours after the return of spontaneous circulation following cardiac arrest in an attempt to prevent cerebral injury.

Hyperthermia

During bacteremia, pyrogens released by bacteria can lead to cytokine (interleukin, IL-1) release. This can lead to a change in the set-point in the hypothalamus, leading to heat conservation (vasoconstriction) and heat production (shivering) producing a fever. Septic patients present with fever, which may persist during anesthesia, especially if the infected tissue is handled during surgery. In inadequately prepared or undiagnosed hyperthyroid patients, thyroid storm may rarely cause hyperthermia. In these patients, despite an adequate anesthetic, tachycardia, hypertension, and hyperthermia (temperature >38°C) are suggestive of thyrotoxicosis.

Malignant hyperthermia (MH) is a rare congenital genetic disorder in which a life-threatening reaction can occur from certain general anesthetic agents. While tachycardia, hypertension, muscle rigidity, and bronchospasm all occur, temperature elevation is a late sign in MH.

In warm climates, in operating rooms without air conditioning, some patients, especially children, and those with pre-existing fever could become hyperthermic when covered with impervious drapes when undergoing long procedures. In this setting, active cooling by either infusion of cold IV fluid and/or blowing ambient air over the extremities may be necessary to keep them normothermic.

Treatment of hyperthermia

1. *Preoperative period*
 - a. Acetaminophen oral or rectal
2. *Intraoperative period*
 - a. Cold water soaked sponges placed over major vessels in the neck, groin and axilla (over the axillary, femoral and carotid artery)
 - b. Active cooling of the operating room
 - c. Forced air cooling using cooling devices that blow cooler air into jackets or blankets placed on the patients skin (torso and/or extremities)
 - d. Circulating water mattress placed over or under the patient for cooling
 - e. Cooled IV fluids
 - f. Cardiopulmonary bypass assisted cooling
 - g. Field irrigation with cold fluids
 - i. Gastric mucosa using cooled saline instilled via a naso-gastric tube
 - ii. Peritoneal or pleural cavity irrigation
 - iii. Bladder irrigation using a three-way urinary catheter
3. *Postoperative period*
 - a. Forced air cooling
 - b. Circulating water mattress in the ICU

SUMMARY

Physiological thermoregulation is a multilevel control system. The initial response to cold begins with vasoconstriction, followed by shivering. Anesthesia decreases the threshold temperature at which these responses occur, facilitates transfer of heat from the core to the periphery by abolishing the tonic vasoconstriction, and decreases heat production by decreasing metabolic activity.

Mild perioperative hypothermia is associated with poor patient outcomes, including increased wound infection and increased length of stay in the hospital. In cooler climates actively warming the patient prior to induction of anesthesia prevents the occurrence of hypothermia. Anesthetists, by playing an active role in maintaining patient normothermia in the perioperative phase, can play an important role in ensuring a positive outcome for the patient.

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Decontamination Procedures for Medical Equipment

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INTRODUCTION

Microbes (bacteria and viruses) can be carried from one person to another on the surface of any equipment that is shared between them unless it is decontaminated between use. They can also be carried on the skin surface which is why handwashing between examining patients is important. Microbes gain access to the body, through open wounds, inhalation of infected secretions or by close contact with mucous membranes. The process by which microbes are passed from one infected person, to cause infection in another, is known as 'cross-infection'.

Cleaning, disinfection and sterilisation are all procedures that are used in the decontamination process.

DEFINITIONS

Cleaning is the process that removes contaminants including dust, soil, large numbers of micro-organisms and organic matter (e.g. blood, vomit). It is an essential prerequisite to disinfection and sterilisation. It also removes the organic matter on which micro-organisms might subsequently thrive.

Disinfection is a process used to reduce the number of micro-organisms but not usually bacterial spores. The process does not necessarily kill or remove all micro-organisms, but reduces their number to a level which is not harmful to health.

Sterilisation removes or destroys all forms of microbial life including bacterial spores. Each instrument or piece

of medical equipment which comes into contact with a patient is a potential source of infection. These are divided into 3 groups of risk, described in Table 1.

TECHNIQUES OF DISINFECTION AND STERILISATION

Before equipment is to be disinfected or sterilised, it should be thoroughly cleaned to remove any visible dirt or secretions. This involves washing with water and detergent (soap). Protective clothing (an apron, gloves and a facemask) should be worn.

Disinfection is best achieved by moist heat such as boiling in water (100°C for 10 minutes at sea level) which kills all organisms except for a few bacterial spores. It is important to remember that the temperature at which water boils decreases with altitude and a longer boiling time will be required. For example, at 4000m above sea level where boiling occurs at 86°C a minimum of 20 minutes is required for disinfection. It is important to note that boiling equipment items in water will not achieve sterilisation.

Disinfection can also be achieved by using chemicals which however may themselves be toxic when allowed contact with skin or are inhaled. They can also be corrosive and flammable so that protective clothing (gloves, apron and a facemask) should be worn. Chemical disinfectants may be supplied ready to use or may need accurate dilution to provide an appropriate solution. It must be remembered that disinfectants

Summary

Decontamination of medical equipment involves the destruction or removal of any organisms present in order to prevent them infecting other patients or hospital staff.

Decontamination reduces the risks of cross infection and helps to maintain the useful life of equipment. It is important in the overall control of hospital acquired infection.

Table 1. Level of risk

High risk items	Items come into close contact with a break in the skin or mucous membranes or are introduced into a normally sterile body area. e.g. surgical instruments, needles, urinary and other catheters. Sterilisation is required for this group.
Intermediate risk items	Items come into close contact with mucous membrane or are items contaminated with particularly virulent or readily transmissible organisms. e.g. Items of respiratory equipment including laryngoscope blades, endotracheal and tracheostomy tubes, oropharyngeal and nasal airways. Disinfection is required for this group.
Low risk	Items only come into contact with normal intact skin. e.g. stethoscopes or washing bowls. Cleaning and drying is usually adequate for this group.

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can decay and lose activity. Decay is more rapid at high temperatures and can be accelerated by the presence of impurities. All disinfectants take time to work.

RANGE OF ACTIVITY OF DISINFECTANTS

Gram positive bacteria (e.g. Staphylococci), are more sensitive than gram negative bacteria (e.g. Pseudomonas). Mycobacteria and spores are relatively resistant. Enveloped viruses (e.g. HIV) are killed by most disinfectants but non-enveloped viruses (e.g. Coxsackie) tend to be more resistant.

Spores

Fungal spores are easily killed by disinfectants. Other bacterial spores (e.g. Clostridia) are resistant to most disinfectants in common use.

Tubercle bacteria

These pathogens are more resistant to chemical disinfectants than other bacteria. They can be killed by exposure to 2% alkaline Glutaraldehyde solution (Cidex) for 60 minutes.

Viruses

Hepatitis B virus (HBV) and Human Immunodeficiency Virus (HIV) are inactivated by Cidex in 1 - 2 minutes, although to ensure adequate penetration, soiled items should be placed in a 2% glutaraldehyde solution for 30 minutes. Exposure to 70% alcohol solution for 10 minutes is also effective. Viruses causing Rabies, Lassa fever and other haemorrhagic fevers are also killed by Cidex.

CHEMICAL DISINFECTANT SOLUTIONS

Clear Soluble Phenolics (e.g. Stercol & Hycolin) are good for killing most bacteria including TB. They have limited activity against viruses.

Hypochlorites (e.g. Presept and Milton)

These agents have a wide range of activity against bacteria, fungi, viruses and bacterial spores. They may be used for decontaminating any area with blood spillage. They are corrosive to metals and must be applied at the correct concentration. They are inactivated by organic matter and decay on storage.

Alcohols (e.g. methanol, ethanol and isopropanol)

Alcohols have good activity against bacteria & viruses. They should only be used after all the visible surface dirt has been removed from the area to be disinfected.

Aldehydes (e.g. glutaraldehyde and formaldehyde)

These agents are active against bacteria, viruses and fungi. They have a slow action against tubercle bacilli and are irritant to skin and eyes.

STERILISATION

This can be achieved by steam, steam and formaldehyde, hot air, ethylene oxide or irradiation. Autoclaving is the commonest method, using steam under pressure and is the most reliable way to sterilise instruments. A temperature of 134°C for 3 minutes or 121°C for 15 minutes is recommended.

Formaldehyde is irritant to the eyes, respiratory tract and skin. It can also be absorbed by some materials and subsequently slowly released with potentially hazardous results. Hot air sterilisation takes a long time and items must be able to withstand temperatures of at least 160°C for periods of 2 hours or more.

Ethylene oxide is a colourless gas which is toxic to inhale. It is effective against all organisms and does not damage equipment. The operating cycle ranges from 2 - 24 hours so the turnaround time is prolonged and it is a relatively expensive process.

Sterilisation by irradiation is an industrial process and particularly suited to the sterilisation of large batches of products. Irradiation can cause serious deterioration of materials and is therefore not a suitable method for the resterilisation of equipment items.

SUMMARY OF DECONTAMINATION PROCEDURES

Respiratory equipment

Sterilisation is unnecessary since spore-bearing organisms are not a cause of respiratory infection. Infection hazards can be reduced by lowering the amount of condensation in a circuit by means of heat-moisture exchangers, moisture traps and by the regular cleaning and drying of valves and circuits.

Many hospitals do not have access to disposable **ventilator circuits** and therefore with mechanical ventilators the internal circuit can often be autoclaved. The external (or patient) circuit and humidifiers may be disinfected in a washing machine at a temperature of at least 71°C for 3 minutes. The external circuit should be changed every 48 hours or between patients. Heated water humidifiers should be cleaned, dried and refilled with sterile water every 48-72 hours. If nebulisers are used they should be rinsed in alcohol after cleaning every 48 hours.

Anaesthetic face masks should be washed and cleaned after each use. Where resources allow single use disposable masks are now recommended.

Laryngoscope blades should be washed after use and disinfected either chemically by soaking in 70% alcohol for 10 minutes, or by thermal means such as boiling in water at 100°C for 5 mins.

Endotracheal tubes intended for single use can be re-used if they are cleaned and disinfected. Thermal methods are likely to cause material damage but following cleaning, chemical disinfection can be provided by immersing tubes in a solution of 70% alcohol for 10 minutes. The tubes should then be allowed to dry before use. 2% glutaraldehyde is not suitable as it may be absorbed by the plastic and is too irritant.

Suction catheters are not easy to clean but provided they are free of visible soiling they may be disinfected using 70% alcohol as described earlier and allowed to dry before use.

Instruments such as needles and cannulae (including spinal and epidural needles) are reused in many resource-poor settings, where the supplies of new equipment are severely stretched. These must be sterilised after thorough cleaning. In many situations autoclaving is the most practical technique.

Fires and Explosions in the Operating Room

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INTRODUCTION

The Operating Theatre/Room (OR) is a potentially dangerous place with regard to fires and explosions, due to the presence of:

- Flammable substances,
- Oxygen and/or nitrous oxide,
- Sources of ignition (flames, sparks).

OXIDATION

The basis of all combustions and explosions is oxidation, which is the chemical reaction between a substance and oxygen. Atoms are broken up and rearranged to form a new compound with the production of energy, mainly in the form of heat but often associated with light, sound, pressure and electricity. This is an exothermic oxidative reaction.

Oxidation can occur in a number of different ways:

Biological oxidation

Glucose, like a number of other carbohydrates, is oxidised in humans consuming oxygen and producing energy (3,700kcal.kg⁻¹). This happens in a very slow and well regulated manner, at a low and almost constant temperature through a series of enzyme reactions. The end point of the reaction is the production of carbon dioxide (CO₂) and water, plus energy, which is dissipated as heat or utilized in other reactions.

Combustion

Alternatively wood under different conditions may burn, consuming oxygen and producing exactly the same amount of heat but in a much shorter time at a higher temperature. Similarly petroleum gases contained in the cylinders for kitchen use can burn in a controlled way in a stove to boil surgical instruments.

Combustibles

These are substances capable of reacting with oxygen to produce heat at high temperatures. Many combustible materials, which include alcohol, cotton fabric, wood and rubber, are present in the operating theatre. For complete combustion to occur there is an ideal proportion of fuel and oxygen, which is defined as a

stoichiometric mixture. For instance, the stoichiometric mixture of diethyl ether vapour in oxygen is one mole (see Appendix 1) of ether (74g) and 6 moles of oxygen (192g) or about 14% ether vapour in oxygen. In air, the stoichiometric concentration of ether is 3.4% and in nitrous oxide it is 8%.

In practice these exact proportions seldom occur. When the concentration of fuel is more than ideal, the mixture is described as 'rich', with some fuel being left either unburned or incompletely oxidised into a range of compounds (e.g. carbon monoxide, or acetaldehyde in the case of ether). When the fuel concentration is less than the ideal, the mixture is described as 'lean' with some oxygen left over. Whether oxidising sugar at body temperature or burning gas in a stove at a much higher temperature, the reaction normally proceeds until either the fuel or oxygen are finished. Moreover there is a balance between the energy produced and the energy, mainly heat, which is dissipated (escapes). The reaction is at an almost constant temperature, called an isothermal reaction. When heat production is faster than dissipation, heat will accumulate and the reaction can enhance itself to the point of an explosion.

Flame

Normally a flame remains confined to a fixed point and is called a static flame - the candle flame, gas burner and spirit lamp are examples. Of more interest is the self-propagating flame, again produced in a lean (1/10 stoichiometric) air mixture inside a tube. This describes a flame, which can travel along leaving behind the products of combustion, whilst the front of the flame heats fresh mixture which in turn ignites and becomes a flame itself. The process is called deflagration, which is generally a mild phenomenon but can become very dangerous if it comes in contact with an explosive mixture.

A very peculiar phenomenon is the production of a cool flame by the oxidation of very rich mixtures of certain volatile agents with air. Ether can form a cool flame at concentrations around 20% to 35% when heated to as little as 200°C. There is a small zone of oxidation (not a real burning) at a low temperature and with barely visible light. The cool flame travels along the mixture, eventually dying off. However the danger is that it can

Summary

This article will explain how fires and explosions develop and the precautions which, when acted upon, help to avoid this serious and sometimes disastrous event. The patient and staff may be injured or killed by a fire or explosion.

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act as a powerful ignition source if it encounters an explosive mixture. In addition it may remain unseen until it is too late! A classic example occurs when ether is spilled on the floor and, because it is heavy, does not spread, forming a very rich localised mixture. A faulty electric plug could then ignite the ether mixture causing a cool flame, which then travels along the floor until it reaches a place where the mixture is explosive, such as the exhaust from an anaesthetic machine, which then explodes.

Activation energy

Energy, usually heat, is needed to start the reaction. This is called the activation energy, which can be provided by an open flame, sparks, hot plate or filament. The activation energy required to start a reaction varies very much, but for ether/oxygen mixture it is very little. In practice it is the temperature of the ignition source, which is measured. The minimum ignition temperature for the most inflammable mixtures of anaesthetic vapours, in air, lies between 400 and 500°C. Note that in oxygen the minimum ignition temperature is some 50°C lower. In contrast, a cool flame may start at a temperature as low as 200°C in a rich mixture of ether in air (20 to 35%).

Reaction Rate

The reaction rate is directly related to the size of the activation energy. Thus, the higher the activation energy the more rapid the reaction rate, and the more likely an explosion. Other factors may influence the initiation and the rate of reaction.

Temperature of the mixture

The speed of the reaction is doubled when the initial temperature is raised by 10°C (Arrhenius law). If the heat generated at the beginning of a reaction is only partially dissipated, the small amount of heat left behind is sufficient to raise the temperature and thus the rate of the reaction. In contrast, when, adequate heat loss occurs, such as in large rooms, the reaction may come to a halt. A self propagating flame, as described above, produced by burning ether in air inside a tube can progressively increase its temperature and pressure causing a powerful deflagration with an explosion of the tube especially if the end is closed. If the tube contains an oxygen rich mixture, a much more powerful event can be produced. Fortunately this requires the combination of a very powerful ignition and a long tube. This cannot be produced in common anaesthetic machines.

Limits of flammability

If the mixture becomes too lean it cannot ignite. The Lower Limit (LL) for diethyl ether is 2.1% (vapour) v/v (volume for volume) in either air or oxygen. There is also an Upper Limit (UL) where there is an excessive concentration of fuel for the oxygen present. The UL for ether in air is 36% v/v and 82% in oxygen.

NITROUS OXIDE

Although N₂O does not enter the biological oxidising processes, it is a powerful oxidant i.e. it strongly supports any combustion process. It is absolutely wrong to assume that it will prevent fires and explosions by dilution of oxygen. It is as effective as oxygen in producing explosive mixtures.

IMPLICATIONS FOR ANAESTHESIA

The conditions for flames and explosions require three essential

components, a combustible substance, a source of ignition and oxygen. Despite the dangers described, in practice they rarely occur in the theatre, provided staff are careful, understand the mechanisms and take the appropriate precautions.

FLAMMABLE SUBSTANCES IN THE OPERATING THEATRE

Diethyl ether

Ether burns slowly in air and is not easily ignited by a spark; mixtures with oxygen and/or nitrous oxide become explosive between approximately 1.5 and 40% v/v. Maximum detonability is approximately 15% in oxygen. Therefore hot wires and plates at 300°C, below the temperature of dull-red visible heat, are sufficient to start an invisible flame. Remember that ether vapour is denser than air and therefore sinks, spreading over the floor. Ether is stored in the dark to prevent auto-oxidation, which can make the simple shaking of the bottle enough to trigger an explosion. Anti-oxidants are added to anaesthetic or laboratory ether, reducing this risk.

Ethyl chloride

Ethyl chloride burns easily and explodes in oxygen or nitrous oxide or air - stoichiometric concentrations are respectively 25%, 14% and 6.5% v/v, with narrow ranges between LL and UL. Ethyl chloride is very dangerous.

Petroleum lubricants

A sudden rise in pressure in a confined area such as a reducing valve or pressure gauge, can generate sufficient heat to ignite petroleum lubricants and cause an explosion.

Alcohol

Alcohol burns very easily with an almost invisible flame, which is easily overlooked. It can easily soak drapes or swabs, which can then be ignited by a diathermy spark, especially in the presence of oxygen or nitrous oxide.

Natural (generally methane or hydrogen) or anaesthetic gases inside body cavities (bowel, or alveoli) as well as swallowed ether in the stomach can explode or be ignited by the diathermy.

Propane, butane or other petroleum gases for burners, stoves, lamps are very common sources of domestic and theatre disasters.

Modern volatile agents

None of these (desflurane, isoflurane, sevoflurane) is inflammable. However they are expensive and not always available. Halothane, which is inexpensive and widely available, is also not inflammable, nor is the azeotropic mixture (halothane 66%-ether 34% - see Appendix 3).

SOURCE OF IGNITION ENERGY IN THEATRE

Extraneous flames

Any kind of open flames from candles, burners, matches, burning lamps etc, however small.

Hot wires and plates

Cautery, electric stoves, hot-wire spirometers, electric bulbs especially those for endoscopy or modern halogen lamps, glowing cigarette ashes.

Electrosurgical appliances

These are powerful sources of ignition energy in the form of sparks, arcs or heat within the machine, the foot switch, diathermy spark, or faulty equipment. Sparks also happen in normally functioning switches, or when a live plug is pulled from a socket. Bad electrical contacts not only produce hot wires and/or arcs, but can also cause a fire themselves.

Static electricity

This is a possible risk, though the risk is reduced in a humid environment. A fully antistatic equipped theatre is ideal but difficult to realise, small measures such as using black rubber antistatic tubing for the breathing tubing and scavenging will reduce the risk.

Compression energy

Gas escaping from cylinder may ignite lubricants.

SAFE CLINICAL PRACTICE

Keep the anaesthetic mixture confined to the apparatus

Avoid open mask anaesthesia

If an open mask technique is used and the head is not covered by drapes, and the room is well ventilated, only an area extending for some 25-30cm around any part of the patient's head should be considered dangerous. Gases passing under the towels toward the diathermy are potentially very dangerous.

Use an endotracheal tube or LMA whenever possible

- Semi-closed breathing systems (e.g. the Penlon EMO vaporiser or Tri-Service apparatus)

Ensure good theatre ventilation

In a well-ventilated room, the mixture is rapidly diluted to a safe concentration once it leaves the expiratory valve of the breathing system or ventilator.

Use a scavenging system

This must be connected to the expiratory valve of the breathing system or ventilator to carry the ether mixture outside through a theatre wall.

Define the 'zone of risk' of fire or explosion

- Described by the Association of Anaesthetists of Great Britain and Ireland in 1971. It is defined as an "area extending 25 cm around any part of the anaesthetic apparatus..." This is because leakage from the apparatus is always possible, but careful maintenance of the apparatus will help to reduce leaks. Potential sources of ignition must not be put in this area.

Diathermy

- Safe to use with ether and air providing you are not working on the head and neck or lungs. There is a risk of a fire, but if it is not used near the head and neck or lungs, the risk of a fire is very small.

Oxygen and ether combinations

Oxygen may be required to maintain the patient's oxygen saturation during anaesthesia (Appendix 2). Under certain conditions a mixture of ether and oxygen can result in an explosion, compared to a mixture of ether and air which can burn. Therefore added oxygen and diathermy is a very dangerous combination. Do not use ether and oxygen with diathermy. You must either switch off the oxygen, or switch off the ether, or ask the surgeon to switch off the diathermy.

Minimize the flammability

- Use as little supplementary oxygen as needed to maintain saturation
- If possible use non-flammable agents
- Store all flammable substances out of the room and in a safe place
- Gas and petroleum burners should be kept out of the theatre - no open flames or fires
- Avoid nitrous oxide.
- Do not use lubricants on reducing valves, pressure gauges or other parts connected with oxygen or nitrous oxide cylinders.
- Dilute any flammable or explosive mixtures, which escape if the air in the room is changed as often as possible - plenty of fresh air. Note that air conditioners like those used for home or office do not change air, in fact they may be a source of ignition.

Prevent ignition sources

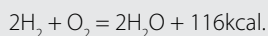
1. Keep monitors, other electrical appliances and instruments 1.5m above the floor and at a safe distance from head of the patient (25cm).
2. Beware of diathermy! Both the electrode and foot switches should not be allowed into contact with anaesthetic gases. Remember these may infiltrate the towels toward the surgical field.
3. Keep all unnecessary electrical apparatus out of the room. The oxygen concentrator can be placed at a distance from the anaesthetic machine and connected by any long tube of 1cm diameter. Alternatively it can be mounted on the wall, 1.5m from the floor.
4. All equipment should be properly earthed at a single point (not the water pipe!) with cables of large diameter and not welded.
5. Any patient ventilator should be flame/explosion proof.

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APPENDIX 1.

A reminder of basic chemical terms and facts



That is two moles (2g) hydrogen (H_2) plus one mole (32g) oxygen (O_2) produces two moles (36g) water (H_2O) and 116kcal of energy.

Atomic weight

The weight of the atom of an element compared to the weight of an atom of hydrogen, which in effect becomes the base unit e.g. the oxygen atom weighs 16 times the atom of hydrogen - the atomic weight of oxygen is 16. Other examples include carbon 12, nitrogen 14 and sodium 23.

Molecular weight

The sum of the atomic weights of a compound: e.g. the gaseous oxygen molecule is formed by two atoms and therefore its molecular weight is $16 \times 2 = 32$; nitrous oxide (N_2O): $(14 \times 2) + 16 = 44$; diethyl ether ($\text{C}_4\text{H}_{10}\text{O}$): $(12 \times 4) + (10 \times 1) + 16 = 74$

Mole

The molecular weight expressed in grams: 1 mole of oxygen = 32g; 1 mole of ether = 74g. One mole of any substance contains the same number of molecules. One mole of any gas ideally occupies a volume of 22.4 litres at *standard temperature and pressure* (0°C or 273°Kelvin : 760mmHg).

Combustion

When combustion is complete, the following reaction occurs:

1 mole fuel + b moles oxygen = products (CO_2 and H_2O) and Energy (heat, light etc).

"b" is the exact number of moles of oxygen required to completely oxidise completely one mole of fuel.

Density

Ether vapour has a density of 2.56 with respect to air.

Appendix 2.

The ether-oxygen dilemma

Ether is still considered a very valuable agent for inhalation anaesthesia, because it is non-toxic, efficient, and inexpensive. It is therefore rightfully still widely used in many parts of the world. However there are difficulties. As with any anaesthetic, there is impairment in pulmonary function, which may require an inspired oxygen concentration above 21% (together with assisted or controlled ventilation). Therefore oxygen supplement may be required, which increases the possible danger of fire or explosion.

Appendix 3. Azeotropic mixture

Halothane 66% and diethyl ether 34% mixed together form an azeotrope or a mixture where the molecules of the components form loose hydrogen bonds and cannot be separated by distillation in spite of different vapour curves.

The halothane/ether azeotrope can be vaporized with a halothane vaporiser and clinically useful concentrations are similar to those of this agent or around 1.5%. Induction is reasonably quick and not unpleasant and recovery is more prompt than with ether. Due to the ether in the mixture, the azeotrope retains powerful analgesic and relaxant properties and like ether it gives excellent cardiovascular and respiratory conditions. It is not explosive, can be easily transported and stored and may burn in oxygen only at concentrations over 10%.

The halothane/ether azeotrope is an excellent anaesthetic which combines the best of the two parent substances. It is surprising that it does not have the recognition it deserves. This is possibly due to the poor development of anaesthesia relevant for developing countries whilst anaesthetists in affluent countries are submerged by a profusion of new molecules.

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Notes

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Notes

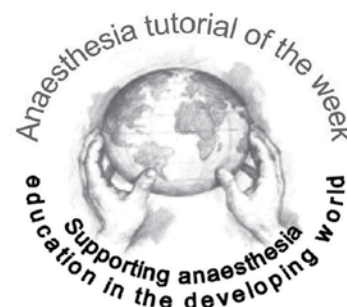
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Update in Anaesthesia

Guide to Contributors

Update in Anaesthesia is primarily an educational journal, which aims to provide ongoing learning and support for anaesthetists working in situations with limited resources.

Update is sent to over 3000 English-speaking anaesthetists, and read by many others including surgeons, nurses and medical students. *Update* is also translated into different languages including Spanish, Russian, French and Mandarin. After being produced in the paper format, *Update* is published on the internet (www.worldanaesthesia.org) and read by 90 people a day from more than 130 countries. *Update* is also distributed in the form of a CD-ROM, produced by the Association of Anaesthetists of Great Britain and Ireland.

Articles for consideration by the Editorial Board should be submitted as Word documents (Rich Text Format is preferred) to the Editor-in-chief, Bruce McCormick, by email at Bruce.McCormick@rdeft.nhs.uk or post on CD-ROM or paper copy to Dr Bruce McCormick, Department of Anaesthesia, Royal Devon and Exeter Hospital, Barrack Road, Exeter, EX2 5DW, UK.

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Please supply the full forename and surname of all authors, stating their title (Anaesthetic Clinical Officer, Dr, Professor etc) and the name and address of their institution. One author should be identified for correspondence, with an email address provided.

Drug doses

Please use the international units, e.g. mg.kg⁻¹ rather than mg/kg. Use SI notation for g, mg, mcg etc. Please use internationally accepted non-proprietary drug names, e.g. furosemide, epinephrine and avoid trade names.

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1. Reynolds F, O'Sullivan G. Lumbar puncture and headache. 'Atraumatic needle' is a better term than 'blunt needle'. *Br Med J* 1998; **316**: 1018.
2. Costigan SN, Sprigge JS. Dural puncture: the patients' perspective. A patient survey of cases at a DGH maternity unit 1983–1993. *Acta Anaesthesiol Scand* 1996; **40**: 710–14.
3. Spriggs DA, Burn DJ, French J, Carlidge NE, Bates D. Is bedrest useful after diagnostic lumbar puncture? *Postgrad Med J* 1992; **68**: 581–3.

References to books should give book title, place of publication, publisher and year; those of multiple authorship should also include chapter title, first and last page numbers, and names and initials of editors. For example:

1. Roberts F. Chapter 22: Ear, nose and throat surgery. In: Allman KG, Wilson IH, eds. *Oxford handbook of Anaesthesia* (1st edition) Oxford: Oxford University Press, 2001: 506–39.

UPDATE SHORT REPORTS

The scope for publication of articles describing original research and audit conducted in, and specifically relevant to, poorly-resourced settings is limited. Successful publication in major journals is rare and the distribution and accessibility of the national and regional journals that currently publish these articles is often poor. As the official journal of the World Federation of Societies of Anaesthesiologists, *Update in Anaesthesia* is the appropriate forum for publication of these manuscripts and offers a wide distribution.

The guidance above for clinical overview articles applies, with the following additional considerations.

Legal considerations

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The editorial team will be delighted to help with the preparation of articles. The best way of doing this is via email - Bruce.McCormick@rdefn.nhs.uk

Dr Bruce McCormick
Editor-in-chief
Update in Anaesthesia, July 2008

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Update in Anaesthesia

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Volume 24 Number 2

December 2008

EDITORIAL

3 Editorial

PHYSIOLOGY

- 6** An Introduction to Cardiovascular Physiology
- 11** Aspects of Myocardial Physiology
- 15** Respiratory Physiology
- 20** The Physiology of Oxygen Delivery
- 22** Carbon Dioxide Transport
- 26** Cerebral Blood Flow and Intracranial Pressure
- 36** The Autonomic Nervous System - Basic Anatomy and Physiology
- 40** The Physiology of Neuromuscular Junction
- 43** Body Fluid Compartments, Sodium and Potassium
- 52** Endocrine Physiology
- 60** Renal Physiology
- 66** Liver Physiology
- 69** Physiology of Pain
- 72** Physiological Changes Associated with Pregnancy

PHARMACOLOGY

- 80** An Introduction to Pharmacology and Drug Doses
- 82** Pharmacokinetics and Anaesthesia
- 86** Pharmacodynamics and Receptor Physiology
- 90** The Pharmacology of the Autonomic Nervous System
- 96** Intravenous Drugs used for the Induction of Anaesthesia

- 102** Pharmacology of Inhalational Anaesthetics
- 108** Pharmacology of Neuromuscular Blocking Drugs and Anticholinesterases
- 112** Paracetamol - A Review of Three Routes of Administration
- 115** Non-steroidal Anti-inflammatory Drugs
- 118** Pharmacology of Opioids
- 125** Local Anaesthetic Pharmacology

PHYSICS AND EQUIPMENT

- 130** Gases and Vapours
- 135** Vaporisers
- 141** The Physics of Flow
- 145** Anaesthetic Breathing Systems
- 150** SI Units
- 151** Humidification
- 154** Anaesthetic Gas Scavenging
- 156** Practical Applications of Pulse Oximetry
- 160** Pressure and Blood Pressure Monitoring
- 164** Biological Signals and their Measurement
- 170** Respiratory Gas Analysis
- 174** Electricity and Magnetism
- 182** Heat Production and Loss
- 188** Decontamination Procedures for Medical Equipment
- 190** Fires and Explosions in the Operating Room

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