DEPARTMENT OF ANAESTHESIA
& PERIOPERATIVE MEDICINE
UNIVERSITY OF CAPE TOWN

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DEPARTMENT OF ANAESTHESIA & PERIOPERATIVE MEDICINE
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A Deep Dive into Medical Gas Supply

A/ Prof. Ross Hofmeyr

Dept of Anaesthesia & Perioperative Medicine
University of Cape Town

Introduction

By the time you have finished reading these notes, you will know how space suits are pressurised, the lowest recorded FiO_2 ever given to working humans, and what happens when you make jokes about noble gasses. None of this will help you pass your primaries, but an understanding of the safe production, storage, supply and delivery of medically-relevant gasses will make you a safer practitioner. Along the way, we'll examine or compare similarities with breathing gas supply for other industries, such as professional and recreational diving.

This is not an exhaustive review. Limited useful resources and references can be found below.

Although a multiple of gases are used for roles within the medical context, only a handful have specific respiratory purposes. These include air, oxygen, nitrous oxide, nitrogen, carbon dioxide, helium and argon. There are also mixtures of gasses used for breathing which have common or proprietary names, such as heliox, Entonox, enriched air or nitrox (EAnx), and trimix. A holistic knowledge of gas supply requires understanding the production, storage, supply, delivery and monitoring of these gasses.[1,2]

At each stage, it is essential to recognize and understand the safety systems and engineering controls in place to ensure safe gas delivery. Description of specific patient-applied as administration systems, such as anaesthetic circuits, demand valves, face masks, nasal cannulae and ventilators is beyond the scope of these notes, and the reader is referred to more specific texts on these subjects.

Measuring gasses

Measurements of gasses in the clinical context are usually described in terms of absolute or gauge pressure when in isolation, and partial pressure or concentration when part of a mixture. For instance, the absolute pressure of air at sea level (standard temperature and pressure) is 101,325 kPa, which includes approximately 20,95 % oxygen, giving a partial pressure of 21,2 kPa. While concentration is an easy concept to understand, it is the partial pressure of a gas which exerts the biological effect, and thus partial pressure is of much more clinical value, especially in situations of changing ambient pressure, such as under hyperbaric or high altitude conditions.[3] For instance, as oxygen becomes acutely toxic over a partial pressure of 1.6 atmospheres, commercial divers working at extreme depths have used inspired concentrations of around than 0,2 % oxygen, while still maintaining an adequate partial pressure to remain healthy and functional.

Measurements should ideally be made and recorded in *Système Internationale* (SI) derived units, of which the most common is kilopascal (kPa). However, use in certain areas of units such as millimeters of mercury (mmHg) and pounds per square inch (psi) persists. For ease of comprehension, comparison and calculation, the following equivalency can be recalled:

1 atmosphere (atm) = 1 bar = 1000 mbar = 100 kPa = 1030 cm H20 = 760 mm Hg = 14.7 psi

Cylinder pressures are measured either relative to the ambient/atmospheric pressure (gauge pressure), absolute pressure; reading zero in a perfect vacuum. Absolute pressure therefore equals gauge pressure plus atmospheric pressure. For practical purposes, gauge pressure is most useful for calculating cylinder duration, as the last atmosphere of gas will not flow out of the cylinder once the pressures equalize.

The contents of a cylinder can be measured in two ways, depending on whether the gas is in liquid or gaseous phase at the storage temperature and pressure. For instance, oxygen, air, nitrogen and helium cannot be liquified at room temperature, and are thus always in the gaseous form in cylinders. Cylinder pressure (multiplied by volume) is thus directly proportional to content, allowing easy

calculation of supply at a given flow rate. Gasses which are liquified at room temperature when under pressure (such as nitrous oxide and carbon dioxide) will remain at constant pressure as the liquid form evaporates during use, until the cylinder is nearly empty. In these instances, the weight of the cylinder can be used to measure content, although this is seldom applied in the clinical setting. Under certain conditions (heavy use, suitable ambient temperature and humidity), cooling of the cylinder from evaporation of the liquid within will cause condensation or ice formation on the outside, which is often limited to the external surface of the portion still filled by liquid, and thus provides a visual indication of remaining content.

Specific measurement devices and techniques are beyond the scope of these notes, and addressed well elsewhere.

Gas Production

Fractional distillation

The majority of bulk oxygen production is through fractional distillation of atmospheric air. Air contains 78,08 % nitrogen, 20.95 % oxygen, 0,93 % argon, 0,04% carbon dioxide and trace amounts of helium, neon, methane, and krypton. In addition, water vapour, dust and contaminants can be found. This is drawn in to the system through particulate filters and then undergoes pressurized desiccation in silica and zeolite filters to prevent contamination or blockage due to freezing of water vapour or carbon dioxide. The remaining gas is supercooled to -183 C, at which point the oxygen (and the tiny fraction of krypton and xenon) has entered liquid phase, and can be drawn off from the bottom of the fractionating column. Once this has been removed, the remaining gaseous mixture of argon and nitrogen is cooled to around -200C, and then slowly allowed to warm above the -196 C boiling point of nitrogen. The pure nitrogen gas is removed from the top of the column; once all the other gases *are gone*, only argon remains.

Oxygen concentrators

Oxygen concentrators are electrically powered devices that produce oxygen by using reversible binding of nitrogen to zeolite. This silicate compound acts as an ion-exchanger, creating a “molecular sieve”. Ambient air is drawn into the concentrator through a dust filter by a motor-driven compressor. Water vapour is captured by silica gel desiccation, aided by a heat exchange mechanism driven by the heat generated by the gas compression. The compressed air is then passed through paired zeolite sieve beds in an alternating fashion, controlled by a solenoid which switches side once or twice a minute to maintain continuous flow. The zeolite binds nitrogen, allowing 90-95% oxygen to pass through into a holding tank. Upon switching, this bound nitrogen is released and flushed back into the ambient air, allowing the process to be repeated indefinitely. Flow from the holding tank to the patient is controlled by a valve.

Oxygen concentrators have the advantages of simple operation, very long service lives (in excess of 10 000 hours), absence of requirement for high pressure or cryogenic systems, and low operating cost. In remote areas, oxygen concentrators can avoid the complex logistics required by LiOx and cylinders. However, they do have disadvantages: flow rates produced are typically low (2 to 10 liters per minute); they cannot operate without electrical power (although some battery-operated examples exist for remote/military use), and the pressure produced (about 70 kPa) is insufficient to use typical ventilators anaesthesia equipment designed to operate on a standard hospital 410 kPa cylinder/pipeline supply. However, draw-over systems are ideal to be used with oxygen concentrators, and some ventilators allow supplementation of FiO_2 with low pressure oxygen.

The astute reader will have recognized that a portion of the inefficiency of oxygen concentrators can be attributed to the 2-5% argon present in the output gas. The effect thereof can be explained by a simple question: Why does no-one laugh when the Queen breaks wind? Simple: noble gases don’t cause a reaction. As argon is inert, it is one of the least biologically active elements, and appears to have no toxic effect. (Of interest, studies of humans breathing argon as part of a gas mixture under very high pressure have show some changes in electrophysiology of the heart, but this is so far from the clinical setting as to be of interest only to extreme physiologists).

An interesting/specialised use of oxygen concentrators is in the creation of normobaric hypoxic environments, which are used to simulate altitude for sports training. A zeolite system is used, but

instead of producing oxygen as the output, they produce nitrogen, in order to regulate a space (tent or room) with sub-atmospheric FiO_2 but normal pressure.

Chemical and electrochemical reactions

For specific applications, oxygen can be produced as by-product of chemical reactions, and in combination with hydrogen through electrolysis of water. The latter is very effective, and the hydrogen produced has commercial value, but is costly in terms of power consumption. Chemical reactions can be used in lightweight systems with long shelf lives, such as the short-term oxygen production for emergency response and remote medicine applications using systems such as EmOx.

Storage & Supply

Cylinders

Nearly ubiquitous in any setting that uses compressed gas, cylinders typically comprise a body, tapered and threaded neck, valve, pressure release device, and often some for of non-interchangeable safety system. They are identified according to varying colour systems (see Figure 1 and Table 1) and come in a wide variety of sizes. An international standard (ISO/R32) is widely used (including in South Africa), but notable exceptions exist (such as the USA). Cylinder bodies are usually made of steel, aluminium or lighter steel/carbon-fibre combination. While steel (marked “3AA”) is the most common material, aluminium cylinders (marked “3AL” or “3ALM”) are of a similar weight due to the increased metal thickness required, but are useful for use in the MRI suite. Cylinders undergo testing according to national guidelines, which typically call for yearly visual internal inspection, and hydrostatic testing to at least 1.5 times their service pressure every 5 years. The standard fill pressure is always below the maximum working pressure of the cylinder, to avoid exceeding working pressure should the cylinder be exposed to warm temperatures. To prevent overfilling of cylinders containing gasses in their liquid form, the maximum content is expressed as the *filling density*, as a proportion of the weight of the cylinder were it to be filled completely with water. For carbon dioxide and nitrous oxide, this is usually 68%.

Table 1. Cylinder colours

Gas type/mixture	ISO standard	USA
Air	White and black	Yellow
Nitrogen	Black	Black
Oxygen	White	Green
Carbon dioxide	Gray	Gray
Nitrous oxide	Blue	Blue
Helium	BRown	Brown

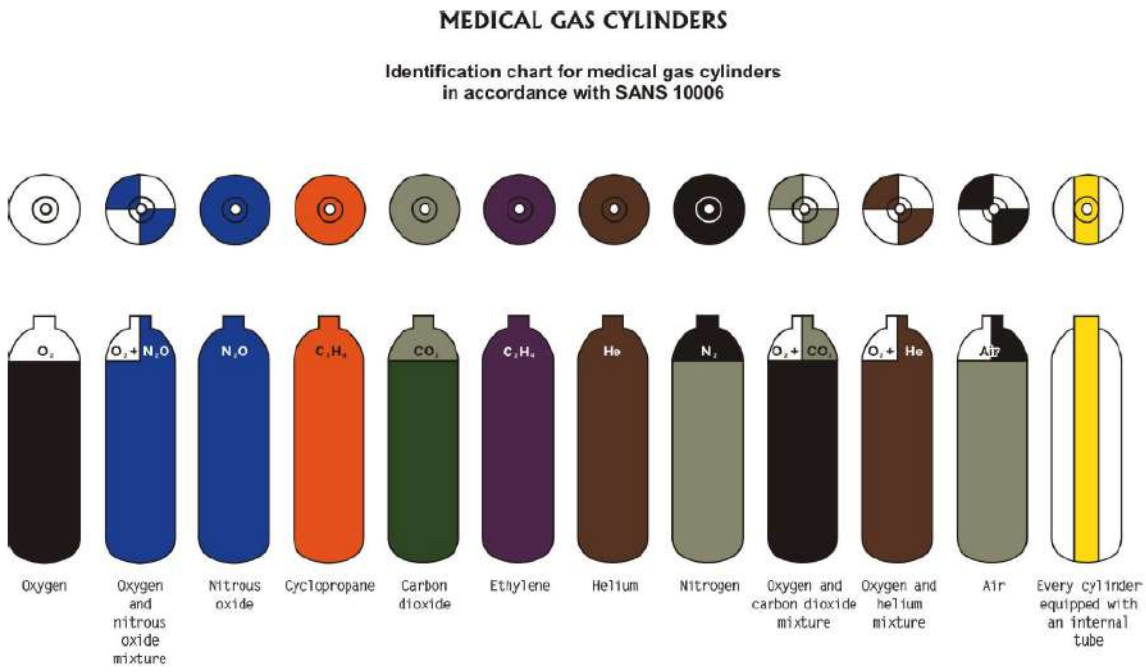

Figure 1. Medical gas cylinder colours in South Africa (SANS 10066)

Cylinder valves incorporate several components, including the port through which gas is released (not to be confused with the pressure release), stem, valve itself, and handle or handwheel. Opening/turning the handle/handwheel allows the stem (shaft) within the valve to lift off its seat, allowing gas flow. The valve either contains packing (usually Teflon) or a diaphragm between the handwheel and stem which prevent gas from leaking. In breathing gas systems, the valve is always opened by rotating the handwheel counterclockwise ("lefty-loosey"). The pressure release device on any cylinder is designed as an initial "point of failure" to prevent catastrophic rupture of the cylinder during accidental over-pressurization during filling, or should a full cylinder be exposed to excessive heat. The simplest form is a *rupture (frangible or burst) disc* which is designed to give way before the cylinder itself fails. *Fusible plugs* are deigned to disintegrate above a specific temperature (rather than pressure), and thus protect against overheating but not overfilling. *Pressure relief valves* are spring-loaded devices designed to vent excess pressure but then reseal, allowing the cylinder to continue to be used. Unfortunately, this comes at a cost of higher complexity and more tendency to leak slowly over time.

Non-interchangeable safety systems for cylinders are an engineering control which extend the safety advantage offered by colour-coding. The *Pin Index Safety System* uses standardized 4 mm diameter pins on the regulator yoke which will only allow the port to seat and seal if the appropriate gas is selected. Limitations include a limited number of pin combinations/orientations, and the possibility of connecting a pin-less regulator to any cylinder. Alternate system is analogous (but not compatible) with the diameter index safety system, where large cylinders have threaded connectors which differ in nipple seat or nose design, diameter, thread orientation (right/left and internal/external), and thread size.

Good practice dictates that cylinders should not be stored where they may be exposed to heat (including direct sunlight), never left standing (where they might cause injury if toppled, or explode or become projectiles if damaged, be opened too rapidly (causing adiabatic cooling) or have any parts (including regulators) exposed to oil or rubber.

Liquid gas storage

It is vastly more efficient to store large quantities of oxygen in liquid form. One kilogram of liquid oxygen (LiOx) occupies a space of about 877 ml, but expands to nearly 755 liters of gas at standard temperature and pressure. Hospitals often maintain bulk LiOx storage in the range of 5 to 50 *tons* in large vacuum insulated evaporators (VIEs). The critical temperature of oxygen is -119 C, above which O_2 cannot be liquified. A typical VIE is maintained at a pressure of around 7 bar and temperature of -

160 C, and functions essentially as a massive vacuum flask. The space between inner vessel and outer shell is kept in deep vacuum to preserve insulation, punctuated by an oxygen gas outlet at the top, and a liquid outlet at the bottom leading to the pressure-raising vaporizer. Oxygen is drawn off at the top via a valve—controlled pressure regulator which steps down to standard oxygen pipeline pressure (4.1 bar). However drawing off oxygen (especially at rapid rates) leads to evaporative cooling inside the VIE. To combat this, liquid oxygen allowed to flow outside the VIE through the pressure-raising vapouriser draws on ambient heat to return the system to stable pressure. Under normal use, the evaporative cooling and vacuum insulation is sufficient to retain the VIE at -160 C. If use is very low, gradual warming can result in increased gas pressure, which is then vented through a safety valve.

Small-container liquid oxygen storage and transport is also used in some countries and practice environments, such as military settings. Advantages include compactness, reduced weight, lower pressures and ease of use. A larger supply container is used to refill portable units, which are much smaller and easier to handle than cylinders. A pressure relief valve allows gas to escape should the flow rate not match pressure build up due to gradual evaporation. For this reason, portable LiOx containers should never be stored in enclosed or sealed spaces. Disadvantages include lower peak flow rates, gradual loss of gas due to evaporation/warming, risk of cryogenic burns due to damage during filling, and equipment freezing if moisture is allowed to enter the couplings or valves.

Pipelines

The challenges and risks of frequently changing cylinders has let to the very common practice of providing pressurized gas pipelines to theatres, ICUs and other areas. The local source may be either liquid storage (in the case of oxygen), or a cylinder manifold. For safety, the bulk storage should be placed in a separate building, or outside. Gas pipelines to clinical areas end in terminal units with non-interchangeable couplings, such as the Schrader valve system. Furthermore, the outlets are color-coded and labelled with the gas type.

A cylinder manifold features two identical banks of cylinders, with each bank able to provide at least two days fo backup supply to the hospital. Coiled copper pipelines connect the cylinders (pressurized up to 137 bar) to a central control box with pressure monitoring and a step-down valve which reduces pressure to around 10 bar. A magnetically controlled changeover valve can switch automatically or manually between banks when the pressure in one back falls below a specified value. A second stage reduction valve on the outlet of the changeover valve reduces pressure further to a standardized 4.1 bar oxygen pipeline pressure. Medical air and nitrous oxide pressures are supplied at under 4 bar, so that any accidental leakage of one gas into another system will always result in *increased* oxygen fraction, rather than a hypoxic mixture. An exception to this is the “HP (High Pressure) Air” connections provided for powering surgical tools such as drills. This has a different non-interchangeable connection from the medical air outlet, and is usually provided from a central compressor at 6.9 bar.

Special cases

Entonox

A 50 %/50 % mixture of nitrous oxide in oxygen which has historically been used as an inhalational analgesic, entonox can be supplied by pipelines (common in labour and delivery units) and cylinders. Because nitrous oxide can occur as a liquid under pressure at room temperatures, cooling an entonox cylinder can result in a liquid phase below the gas which contains approximately 80% N_2O and 20% oxygen. This can occur at temperatures as high as -6 C, which is quite feasible in some parts of the world if cylinders are stored outside, or if a cylinder is allowed to vent rapidly. The initial gas which is drawn from such a cylinder will have a high oxygen concentration, but this will fall as the oxygen passes out of liquid phase, eventually resulting in a hypoxic mixture. Entonox cylinders thus may have *dip tubes* which draw any liquid first from the bottom of the cylinder (providing it is upright!), but the simplest method to avoid this risk is to keep Entonox cylinders at normal room temperatures.

Medical grade air

Medical grade air is counterintuitively produced by the combination of pure oxygen and pure nitrogen in a ratio of 21 to 79 %, and is thus free of impurities, including water vapour, argon and other trace

gasses such as carbon dioxide. As described above, medical grade air outlets should not be allowed to be confused with high pressure compressor-supplied air for powering equipment.

Space suits

If the reader has understood the above content, it will be easy to understand how and why space-suits are pressurized. Clearly, for working in space, a suit which provides a breathable atmosphere and protects against the freezing vacuum while still allowing adequate movement and dexterity is essential. The greater the pressure within the suit, the more resistance to movement will occur. Space suits, therefore, are pressurized to around 28 to 30 kPa, similar to the ambient pressure on the summit of Everest. If containing air, this would lead to severe hypobaric hypoxia, and rapid limitations on physical function. Suits are thus pressurized with pure oxygen, maintaining normoxia (or slightly supranormal levels, as would be found in most patients under anaesthesia receiving an FiO_2 of 30%. This produces a further complication: in the transition from the spacecraft or station pressure (approximately 1 atmosphere of air) to the suit pressure can cause decompression sickness, as nitrogen in the tissues comes out of solution and forms bubbles. To circumvent this, astronauts must perform several hours pre-breathing of pure oxygen at normal atmospheric pressure to off-gas the nitrogen before performing a spacewalk.

Summary

Medical gasses are potent therapeutic agents with dosages which range from the minimum required to cause a biological effect, to toxic levels. It is crucial to understand the relationship between gas concentration and partial pressure, and the safeguards in place to prevent inadvertent administration of harmful gas combinations, especially hypoxic mixtures. Basic safety precautions based on the understanding of the design, function and hazards of gas storage and delivery systems is essential to safe anaesthetic practice.

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Notes

Anaesthesia Breathing Systems and Scavenging

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Anaesthesia Breathing Systems

INTRODUCTION

Anaesthesia breathing systems date back to the very first anaesthetics given. When William T G Morton anaesthetised G Abbot for his jaw tumour excision on 16-10-1846, he used an ether-soaked sponge (the vaporiser) contained in a glass bulb with a mouthpiece (the breathing system). The early systems incorporated a vaporiser in their design, e.g. the Schimmelbusch mask, the Clover inhaler, etc., but with the development of the Boyle's machine (1917), the breathing system became a separate unit.

The function of an anaesthesia breathing system is to allow the normal gaseous exchange to take place, as well as permitting the controlled delivery of our anaesthesia gases.
The prime requirements of such a system are:-

i) Predictable delivery of Oxygen (O_2) and Anaesthetic (AA) vapours,
ii) Efficient removal of Carbon Dioxide (CO_2),
and iii) Be able to monitor and / or control ventilation.

Secondary factors of concern are:-

iv) Economy of gases and anaesthetic vapours,
v) Simplicity and convenience of use,
vi) Ease in cleaning,
vii) Humidity and thermal control,
and viii) Minimise theatre pollution.

CLASSIFICATIONS

Numerous classifications for the breathing systems have been proposed over the years, with little agreement between authors on terminology, resulting in a trans-Atlantic difference in the way breathing systems are classified. The Conway-type classification is favoured by the UK and Europe, and the Dripps et al-type classification by the USA

Conway (1970)

OPEN	System with infinite boundaries. e.g. Insufflation.
SEMI-OPEN	Restricted boundaries with some restriction of fresh gas entry. e.g. Open drop (Schimmelbusch).
SEMI-CLOSED	Fully bounded with venting of excess gas. e.g. Mapleson systems, Circles with > basal flow.
CLOSED	Fully bounded with no venting of gas. e.g. Circle at basal flow

Dripps et al (1968)

INSUFFLATION	System with no Reservoir, Re-breathing, CO_2 Absorption or Valves.
OPEN	No Re-breathing or CO_2 Absorption, but has Valves. It may or may not have a Reservoir. e.g. Non-re-breathing systems (with reservoir) and Demand systems (without reservoir).
SEMI-OPEN	Partial re-breathing and no CO_2 Absorption. Reservoir and Valves may or may not be present. e.g. Open drop (no valve no reservoir), Mapleson systems (A to D - reservoir and valve, F - reservoir only and E - neither).
SEMI-CLOSED	Partial re-breathing with CO_2 Absorption, Reservoir and Valves. e.g. Circle or Water's canister, with > basal flow.
CLOSED	Complete re-breathing with CO_2 Absorption and Reservoir. Valves may be present. e.g. Circle at basal flow (valved), Water's canister (no valves).

The following table shows eight classifications that have been proposed in the past.

System Þ Author ß	Insufflation	Open-drop	Non-re-breathing	Ayre's T piece	Mapleson A-D, F	Water's	Circle
McMahon (1951)	Open	Open	Open	Open Semi-closed	Open Semi-closed	Semi-closed Closed	Semi-closed Closed
Moyers (1953)	Open	Open Semi-closed	Semi-open	Open Semi-open Semi-closed	Semi-open Semi-closed	Semi-closed Closed	Semi-closed Closed
Adriani (1962)	Insufflation	Open	Semi-closed	Semi-closed	Semi-closed	Semi-closed Closed	Semi-closed Closed
Collins (1966)	Open	Open Semi-open	Semi-closed	Open Semi-open	Semi-closed	Semi-closed Closed	Semi-closed Closed
Hall (1966)	Open	Open Semi-open		Semi-closed Semi-open	Semi-closed	Semi-closed Closed	Semi-closed Closed
Dripps et al (1968)	Insufflation	Semi-open	Open	Semi-open	Semi-open	Semi-closed Closed	Semi-closed Closed
Conway (1970)	Open	Open Semi-open	Semi-closed	Semi-open Semi-closed	Semi-closed	Semi-closed Closed	Semi-closed Closed
Baraka (1977)	Open	Open	Open Semi-open	Open Semi-open	Semi-open	Semi-closed Closed	Semi-closed Closed

Table 1 *Classifications of Anaesthesia Breathing systems.* ***Confusion reigns!***

To avoid further confusion, a **functional** classification has been devised by D Miller, which does not use the traditional terminology, and is based on the:

Flow direction- *Uni-directional* or
Bi-directional
Presence or **Absence of a CO_2 Absorber** and
Reservoir bag position - *Afferent* (proximal, fresh gas) limb or
Efferent (distal, exhalatory) limb or
Junctional, i.e. between the 2

Systems in each subgroup have similar fresh gas flow requirements and performance characteristics.

Minimum fresh gas flow ($\dot{V}_F$) requirements for: **Spontaneous**- ß & **Controlled-** ß ventilation			
A) Systems with CO_2 absorption			
i) Uni-directional ö			Circle systems
ý $\dot{V}_F$ is relatively unimportant			
ii) Bi-directional ø			Water's To-and-Fro Canister
B) Systems without CO_2 absorption			
i) Uni-directional			
a) Non-re-breathing valve systems	$1\times\dot{V}_E$	$1\times\dot{V}_E$	Ruben, Laerdal, Ambu, etc. & Demand systems.
b) Circle systems	$1 + \dot{V}_E$	$1\times\dot{V}_E$	
ii) Bi-directional			
a) Afferent Reservoirs			
1. Simple-	$0,7 - 1\times\dot{V}_E$	$2\times\dot{V}_E$	Magill, Lack, Miller PF
2. Displacement- *	$0,7 - 1\times\dot{V}_E$	$0,7\times\dot{V}_E$	Miller E-AR and E-EAR
b) Junctional Reservoirs	$1,5 + \dot{V}_E$	$1,5\times\dot{V}_E$	Mapleson B and C
c) Efferent Reservoirs	$2 - 3\times\dot{V}_E$	$1\times\dot{V}_E$	Mapleson D - F, Bain's

$\dot{V}_E$ = Minute volume at rest» ± 70 *mL kg^{-1} min^{-1}* $0,7\times\dot{V}_E$ » Alveolar Minute volume » ± 50 *mL kg^{-1} min^{-1}*

***** - Sub-group renamed from **Enclosed Afferent Reservoir** to **Displacement Afferent Reservoir** to accommodate Miller's **Enclosed-efferent Afferent Reservoir** system (E-EAR - Maxima^{Ó}).

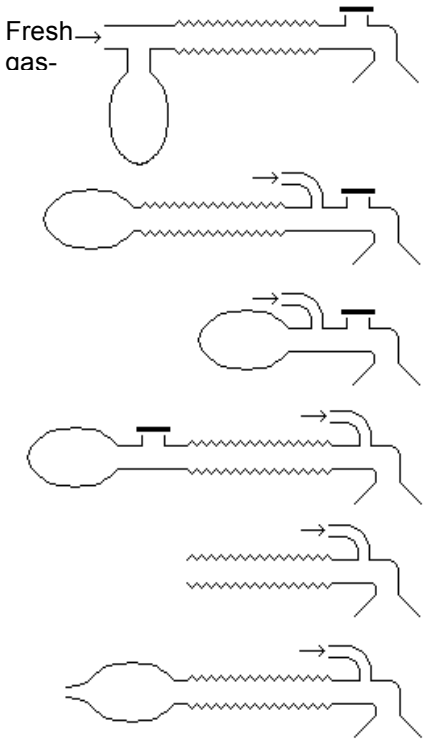
Insufflation & Open-drop techniques are not mentioned, and are probably a subgroup of **B) ii)** *d) No Reservoir*

Table 2 *Miller's Functional Classification for Anaesthesia Breathing Systems.*

W Mapleson (1954) classified the various re-breathing systems, according to the position of the components of a Magill system, and this nomenclature is still widely used.

Five different arrangements were proposed, labelled A to E.
A sixth, labelled F, was added (1975) to accommodate the Jackson-Rees modified Ayre's T-piece.

Mapleson systems are highly dependent on fresh gas flow to limit re-breathing to acceptable levels.



A Magill system (1928)
Lack system (1976)
Miller's Preferential flow system (1979)
Humphrey system in A mode (1981)

B Obsolete

C Water's system - Obsolete for anaesthesia, but still used for resuscitation and transport.

D "Classic" Mapleson D system
Bain's system (1972)
Humphrey system in D mode

E Ayre's T-piece (1937)

F Jackson-Rees modified Ayre's T-piece (1950)

Fig. 1 *Mapleson classification (1954).*

Numerous modifications of the Mapleson systems have been developed.

BASIC PRINCIPLES

A) DEAD-SPACE
Various definitions exist.

Anatomical	That part of the airway where no gaseous exchange occurs.		
Physiological	As above, plus any areas of high $\dot{V}:\dot{Q}$ (i.e. wasted ventilation). This may be dependent on the breathing rate.		
Apparatus	i)	Static	Direct extension of the Anatomical dead-space created by the apparatus in which equal to and fro movement occurs. It comprises the volume in the mask, catheter mount, connectors, etc., up to the part which contains fresh gas.
	ii)	Dynamic	The dead-space that may arise in a breathing system during use, e.g. a T-piece, with too low a gas flow with to and fro movement where it should be uni-directional. This increase in the dead-space due to inadequate gas flow or poor design is a major cause of hypoxia and / or hypercapnia. Dynamic Apparatus dead-space may be less than the Static Apparatus dead-space if streaming or laminar flow is present.

B) RE-BREATHING
Many systems utilise re-breathing to facilitate economy of gas use.
The composition of the re-breathed gas is important.

Dead-space gas	This may be re-breathed to the advantage of the patient, as it has a fresh gas composition and is humidified and warmed.

Alveolar gas — This should preferably not be re-breathed into the patient's gas-exchanging airways as it has a
reduced $P_{I\ O_2}$,
reduced $P_{I\ \text{Anaes. Agent}}$,
and a raised $P_{I\ CO_2}$,
but it could be re-breathed into the dead-space, conserving fresh gas.

In spontaneously ventilating patients, re-breathing of CO_2-containing gas, results in an increase in minute volume, which will maintain normocapnia. The capnograph will only show an increased baseline, peak levels remain constant. There is a limit to the extent that a patient will compensate for re-breathing, after which a progressive rise in both baseline and peak levels occur, possibly leading to dangerous hypercapnia.

This is of great significance in the patient incapable of mounting a response. An increase in the minute volume implies an increase in the work of breathing, which is already raised because of the increased resistance of the system. Patients who typically run into problems are neonates, pulmonary cripples and those with muscle weakness.

With controlled ventilation, however, the patient is not expending any energy, and re-breathing of CO_2-containing gas does not result in an increase in the work of breathing.
It is important to realise that with the re-breathing systems, the minute volume should be increased to compensate for the hypercapnia (± 1,5 x that normally used). A degree of re-breathing is acceptable (even desirable) with controlled ventilation, providing this remains predictable. The limitation to re-breathing with controlled ventilation is whether the pH and / or Pa CO_2 are acceptable.

C) EFFICIENCY OF BREATHING SYSTEMS
The efficiency of a breathing system is dependent on the mode of ventilation.

Controlled ventilation — Efficiency may be expressed as the Fractional Utilisation of fresh gas. It is the fraction of delivered fresh gas that enters the Alveolar compartment and is available for gas exchange. Without CO_2 absorption, it cannot exceed 1,0 or 100 %.

Spontaneous ventilation — The prime requirement of a breathing system is the prevention of re-breathing of CO_2-containing gas; and efficiency is determined by minimising the apparatus dead-space, selective elimination of alveolar gas and decreasing the resistance.

D) RESERVOIRS
Ventilation is a 2-stage process – Inhalation and Exhalation, which cannot occur at the same time as both processes, use the same airway. Exhalation is usually 2 to 4 x longer than inhalation allowing only 20 - 33 % of the time for inhalation. To deliver the normal Minute Volume (≈ 6 L min^{-1} for an adult) will require a flow of 18 - 30 L min^{-1}, but anaesthesia machines (with the exception of draw-over machines) provide a *continuous flow,* not the *intermittent flow* required for ventilation.

There are essentially 3 ways to manage this:

a) Provide the required flow - A “free-flow” system. This is not suitable for anaesthesia as vaporisers and other equipment are not reliable or accurate at such flows. It’s inefficient, expensive and *very* polluting (67 - 80 % of the gas and agents never get to the patient).
b) Utilising a “demand-flow valve” similar to the valve used by scuba divers. Again, the high flow generated is too high for anaesthesia vaporisers. Anaesthesia machines using this principle were used in the past, but it is now confined to the administration of Entonox.
c) The use of a reservoir to accumulate the gas from the anaesthesia machine (after it has gone through the vaporiser) during exhalation (when the patient can’t use it) and having it available for inhalation. The volume of the reservoir must be larger than the tidal volume. The most common reservoir is the familiar bag seen on most breathing systems, but the original Ayre’s T-piece used an open-ended corrugated tube. The required flow of 18 - 30 L min^{-1} is now available.

Secondary functions of the reservoir bags are:

Visual indication of spontaneous ventilation
Manual positive pressure ventilation
Checking for leaks of the breathing system and machine
As a positive pressure limiter, as modern bags are designed to not allow pressures > 40 hPa

INDIVIDUAL BREATHING SYSTEMS

Systems without CO_2 absorption

BI-DIRECTIONAL SYSTEMS

Afferent Reservoirs

A) Simple Afferent Reservoir Systems (Mapleson A systems)

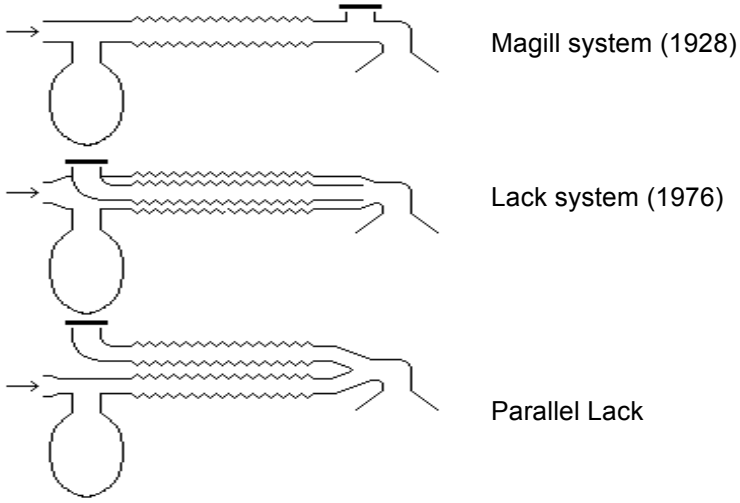


Fig. 2 *Simple Afferent Reservoir Breathing Systems (Mapleson A systems).*

a) MAGILL SYSTEM (1928)

Still popular, especially in more rural or smaller hospitals, because of its simple construction. Advantages include simplicity and good conservation of gases if breathing spontaneously; but not suitable for controlled ventilation, when it requires a very high fresh gas flow. Difficult to scavenge.

The following diagrams demonstrate how this system conserves dead-space gas and preferentially vents alveolar gas with *spontaneous* ventilation.

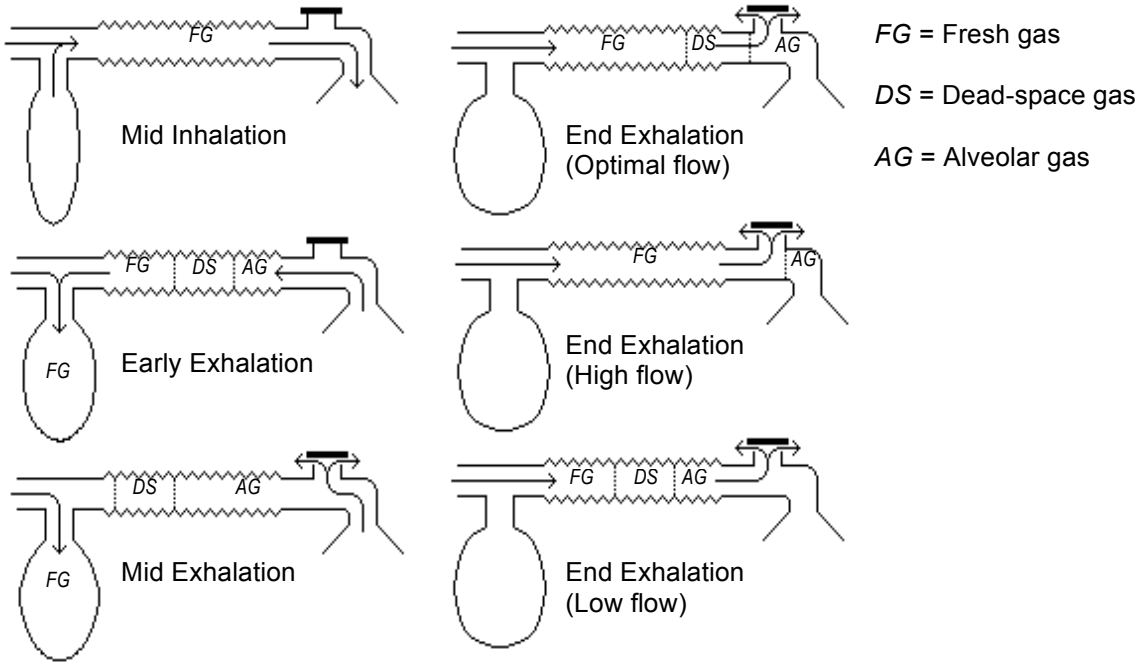


Fig. 3 *Selective venting of alveolar gas by Afferent Reservoir Systems.*

The next diagrams demonstrate why this does not happen with *controlled* ventilation.
The adjustable pressure-limiting (APL) valve must be **partially** open and has a high opening pressure.

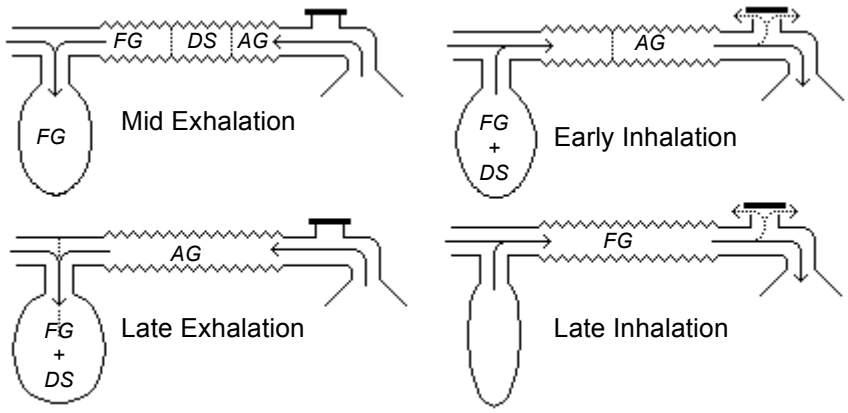


Fig. 4 *Controlled Ventilation with Afferent Reservoir Systems.*

Theoretically, with spontaneous ventilation, Magill systems will selectively vent all the alveolar gas and conserve dead-space gas if optimal fresh gas flows are used; i.e. a Fractional Utilisation of 1,0.
This is estimated at ± 50 mL kg^{-1} min^{-1} (3 - 4 L min^{-1} for an adult) or the Alveolar Minute volume.
With controlled ventilation, dead-space gas, alveolar gas and fresh gas are mixed in the reservoir bag and then partially re-breathed and vented. Only high fresh gas flows with **hyperventilation** will prevent significant re-breathing.
2 x the Minute volume has been recommended as the minimum (9 - 12 L min^{-1} for adults).

The Magill system is best used for spontaneous ventilation in patients over 20 kg in weight. The major drawback is that the APL valve is near the patient and hence difficult to scavenge.

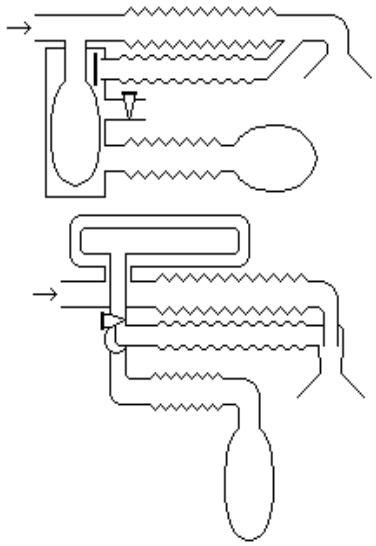
b) LACK SYSTEM (1976)

A modified Magill system with co-axial tubes that allows the APL valve to be positioned away from the patient. It functions exactly the same way as a Magill, and may be even more efficient, because of better sequestration of gases. Scavenging is easy, as the valve is at the machine end.
The **inner *exhalation*** tube (cf. Bain's system) must have low resistance and corrugated tubing is used. The **outer *fresh gas*** tube is consequently larger than normal, making the system bulky.

The PARALLEL LACK is a recent modification, using non co-axial, light-weight tubing, thereby overcoming the bulkiness of the original Lack system.

Numerous modifications of the Mapleson A system have been developed over the years, e.g. HAFNIA, SAMSON, MILLER PREFERENTIAL FLOW, etc., most modifying or omitting the valve.

B) Displacement Afferent Reservoir Systems



Enclosed-Afferent Reservoir system
E-AR
(Miller 1988)

Enclosed-Efferent Afferent Reservoir system
E-EAR or Maxima^{O}
(Miller 1990)

Fig. 5 *Displacement Afferent Reservoir Systems.*
The Displacement Afferent Reservoir systems were designed to produce the same advantageous gas utilisation that the

Mapleson A systems have in spontaneous ventilation, with controlled ventilation; and thereby produce an efficient universal breathing system that only requires the minimal amount of fresh gas (i.e. Alveolar minute volume) as well as maintaining humidity and preventing heat loss.

The MAXIMA$^{\dot{O}}$ system (D Miller, 1995) appears to have all the attributes of the ideal anaesthesia breathing system, although it cannot be called a "simple" system.

Fractional Utilisation of fresh gas approached 90 % (cf. Bain's system ± 70 %) and resistance is minimised by the use of a preferential flow F-piece, removing the resistance caused by APL valves. Conservation of heat and humidity approaches that of a low flow CO_2 absorption system, and may even be superior in the first hour.

The system is designed as a "disposable" system, but may be microwaved for re-use.

Fresh gas flow for both spontaneous and controlled ventilation is Alveolar minute volume or 0,7 x Minute volume (Minute volume » 70 mL kg^{-1} min^{-1}) or 3 - 4 L min^{-1} for adults.

It has not been widely accepted and the resurgence of the circle system rendered it uneconomical.

Efferent Reservoirs

These are the so-called T-pieces and all behave in a similar manner.

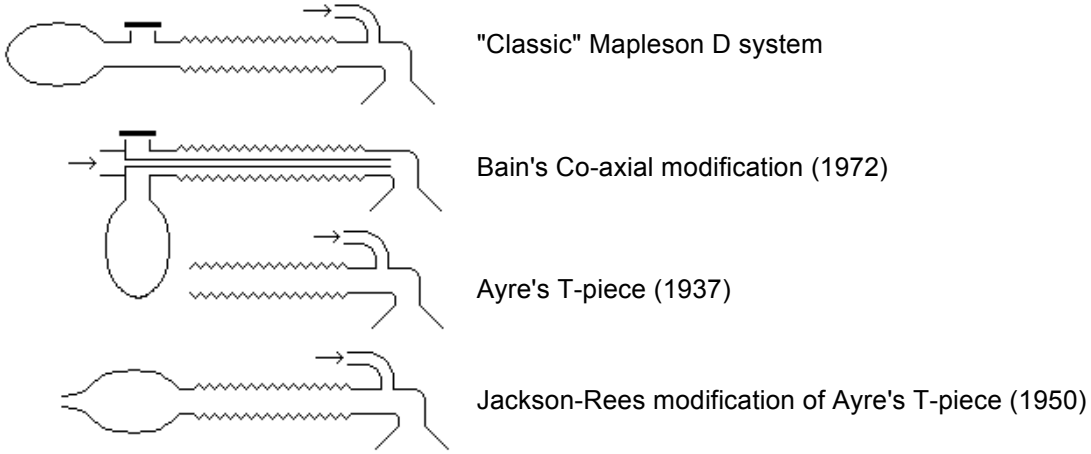


Fig. 6 *Efferent Reservoir Systems*

Whilst the Magill (Mapleson A) system is very efficient for spontaneous ventilation, it is very inefficient for controlled ventilation. The T-pieces are more efficient for controlled and relatively inefficient for spontaneous ventilation, but were frequently used for this purpose (esp. Bain's system).

a) "CLASSIC" MAPLESON D SYSTEM

Not used much in this form, Bain's system being more popular. Fractional Utilisation of Efferent Reservoir systems during controlled ventilation is ± 70 %, but significant CO_2 re-breathing occurs with the recommended fresh gas flows. This is of little consequence with controlled ventilation and may be beneficial, allowing us to hyperventilate patients and reduce intra-operative atelectasis, hypoxia etc., without producing hypocapnia.

The following diagrams demonstrate the gas distribution during spontaneous ventilation.

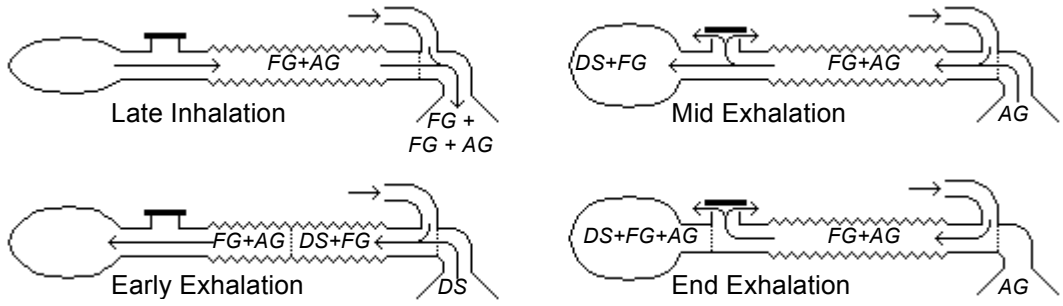


Fig. 7 *Dilution of Exhaled Gases by Efferent Reservoir Systems.*

Dilution is similar with spontaneous and controlled ventilation. With controlled ventilation, using a ventilator, the APL valve is closed and venting occurs via the ventilator valve. With manual ventilation it is partially open.

The extent of dilution of exhaled gases is entirely dependent on the fresh gas flow.
To completely prevent re-breathing during spontaneous ventilation, the fresh gas flow needs to exceed the Peak Inhalation flow of the patient, usually in excess of 25 L min^{-1}. The last portion of inspired gas remains in the dead-space and this allows us to reduce fresh gas flow to a certain extent.

Hyperventilation reduces the CO_2 accumulation and will permit lower fresh gas flow with controlled ventilation, but this is unacceptable for spontaneous ventilation, as it increases the work of breathing.

Optimal fresh gas flow for controlled ventilation is controversial, and dependent on many factors, e.g. breathing pattern, rate, etc., with many authors recommending differing values.
The generally accepted minimum fresh gas flows are:

2,5 (or 2 - 3) x Minute Volume for spontaneous ventilation and
70 mL kg^{-1} min^{-1} for controlled ventilation with **normocapnia** or
100 mL kg^{-1} min^{-1} for controlled ventilation with **mild hypocapnia**.

With controlled ventilation, the Minute Volume should be 1,5 x the fresh gas flow.

b) BAIN'S CO-AXIAL MODIFICATION (Bain and Spoerel, 1972)

The double tube arrangement of the "Classic" Mapleson D system made it rather cumbersome (cf. Magill), hence the development of a single tube co-axial version of the Mapleson D arrangement. It functions in an identical fashion and the same fresh gas flows are required.
It has the advantage of conserving heat to a greater degree than the classic system

A disadvantage, is the possibility of the inner tube coming adrift at the machine end, resulting in an enormous increase in apparatus dead-space, with massive re-breathing (potentially lethal). For this reason, the system has a *transparent* outer tube and a *coloured* inner tube.

Prior to use, the integrity of the inner tube needs to be checked with a suitable test:-

i) O_2 Flush test (Pethick)
The **filled** reservoir bag should collapse if the O_2 flush button is depressed.
This is the result of the Venturi effect at the patient end with high gas flow.

ii) Inner tube Occlusion test (Ghani)
Occlusion of the **inner** tube (e.g. with a 2 mL syringe plunger) results in the Rotameter bobbin "dipping" and a "hiss" should be audible on release.

iii) It is possible to check the integrity of the inner tube by having a coupling in the outer tube and tugging on the inner tube.

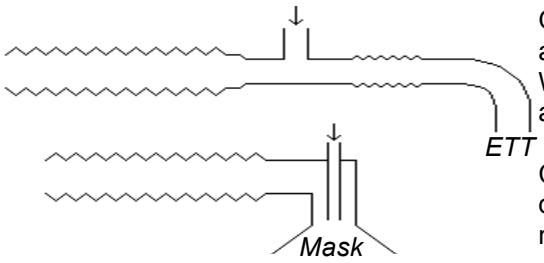
N.B. The normal occlusion test used for other systems does not check **inner** tube integrity. Disconnection of the patient end has no serious consequence.

The Bain's system is functionally very different from the co-axial Lack system described earlier and the inner tube is narrow and smooth, unlike the Lack, and gas flows are reversed. This results in a relatively lightweight and flexible system.

The Bain's system became very popular, and was often the only system available in many UK theatres, even for spontaneous ventilation, although this is not economical.

c) AYRE'S T-PIECE (1937)

This system was designed for anaesthesia for paediatrics (cleft plate repair) with spontaneous ventilation and **intubation**, but has been used (often inappropriately) with a mask. The original T-piece did have a significant dead-space, and numerous adaptations were developed to minimise this.



Original Ayre's T-piece for endotracheal paediatric anaesthesia with a large Apparatus dead-space.
With an endotracheal tube, the dead-space would be acceptable for spontaneous ventilation

Cape Town modification of the T-piece, minimising the dead-space to permit spontaneous ventilation with a mask.

Fig. 8 *Apparatus dead-space with Mapleson E Systems.*

The lack of an APL valve results in a very low resistance, making it imminently suitable for paediatrics. The Efferent reservoir is in the form of corrugated tubing, and its volume must be greater than the Tidal Volume, to prevent entrainment of ambient air.
A disadvantage of this system is the difficulty in monitoring ventilation, as there is no bag to observe. Scavenging is also difficult.
Manual or Ventilator controlled ventilation is simply a matter of occluding the open end of the reservoir tube for inspiration and releasing it for expiration.

d) JACKSON-REES MODIFICATION OF AYRE'S T-PIECE (1950)

The addition of an open-ended reservoir bag to the Ayre's T-piece, makes the entrainment of ambient air unlikely, makes the monitoring of ventilation simpler, makes scavenging easier and permits accurate manual controlled ventilation and / or PEEP.

Most modern T-pieces use lightweight plastic connections suitable for paediatric use, have acceptable apparatus dead-space and provide sampling / suction ports.

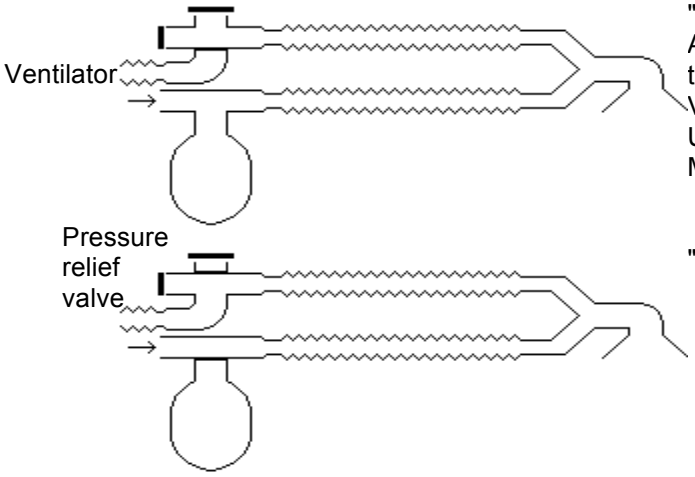
This modification of the T-piece has become the universal paediatric anaesthesia breathing system.

Combination systems

As has been noted, the most efficient breathing system for spontaneous ventilation is a Mapleson A system (probably the Lack); whilst controlled ventilation is best done with a Mapleson D type system. This has resulted in numerous combination systems being developed to cater for both, without having to change systems and / or gas flows. The most popular system is the Humphrey ADE.

HUMPHREY'S ADE SYSTEM (1981)

Developed by D Humphrey of Durban. It's a "universal" breathing system incorporating the Lack (Mapleson A) and Bain (Mapleson D) systems. Available in co-axial (heavier) and parallel versions.



"A" mode (Lever in UP position)
Afferent reservoir bag and APL valve are in the system
Ventilator hose is out of the system.
Used for SPONTANEOUS and short-term MANUAL ventilation.

"D" mode (Lever in DOWN position)
Ventilator hose in the system
Afferent reservoir bag and APL valve out of the system.
Used for CONTROLLED ventilation.

Fig. 9 *Humphrey's ADE system in "A" and "D" modes*

Fresh gas flows that are required are those for the respective breathing system in use, i.e. for:
Spontaneous ventilation 50 mL kg^{-1} min^{-1}
and Controlled ventilation 70 mL kg^{-1} min^{-1} to maintain normocapnia
or 100 mL kg^{-1} min^{-1} for mild hypocapnia.
If 70 mL kg^{-1} min^{-1} is used, there is no need to change flow when converting from one mode to the other, and still use an economical gas flow. A minimum fresh gas flow of 3 L min^{-1} is recommended and the Minute Volume should exceed 1,5 x the fresh gas flow.

UNI-DIRECTIONAL SYSTEMS

These are the Non re-breathing- and Demand- valve systems, and the Circle without CO_2 absorption.

Non re-breathing valves are used in manual resuscitators (e.g. Ambu bag) and anaesthesia systems with them exist (e.g. Tri-tec). The Manley ventilator has a non re-breathing system.

Demand systems are not used much in anaesthesia, but Entonox is supplied by such a system.

The Circle system without CO_2 absorption is illogical with no advantage.

Systems with CO_2 absorption

BI-DIRECTIONAL SYSTEM

WATER'S TO-AND-FRO CANISTER (1924)

The Water's To-and-Fro canister was the first attempt at using a completely closed system with total re-breathing using soda-lime to remove CO_2 from the expired gas. It was used successfully for a number of years, but became obsolete with the development of the Circle system.

It's main disadvantages were the weight of the system (which had to be held on the face by the anaesthetist), the increasing dead-space as soda-lime was used up and the inhalation of caustic soda-lime dust by the patient (as a result of the proximity of the canister to the patient). It did have the advantage of superb humidification and warming of the inspired gas.

UNI-DIRECTIONAL SYSTEM

CIRCLE SYSTEM (Sword, 1926)

This is the only breathing system that can truly be called a "circuit".

An improvement on Water's system, using uni-directional valves and a remote soda-lime canister. Cyclopropane (1930) made this a popular circuit at the time (particularly in the USA) as Cyclopropane was very expensive and *explosive*, necessitating a "closed" system.

Recently, the Circle system has become the dominant anaesthesia breathing system for similar reasons - the introduction of costly inhalational agents and concerns about theatre pollution.

It requires much lower fresh gas flows than even the most efficient non-CO_2 absorption system.

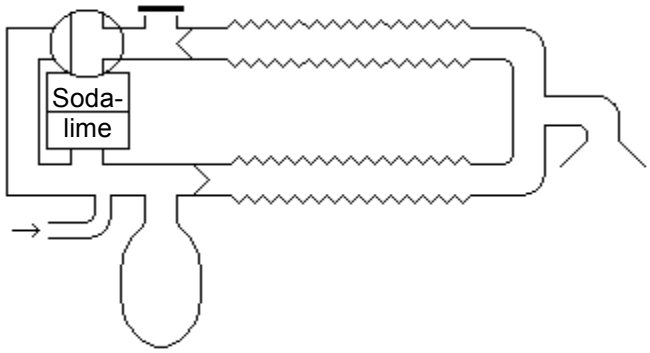


Fig. 10 *The Circle system*

The arrangement of components may be varied, each variation having minor advantages with spontaneous, manual or controlled ventilation.
E Eger (1974) determined 3 rules that must be fulfilled:

i) The reservoir bag must have both uni-directional valves between it and the patient
ii) Fresh gas may not enter the circuit between the exhalation uni-directional valve and the patient
iii) The APL valve may not be between the patient and inhalation uni-directional valve

Advantages of the Circle system include the following:

i) Economy in the use of gases and anaesthetic agents
ii) Increased humidity and warming of the inspired gases
iii) Less pollution and easy scavenging
iv) Facilitation of measuring O_2 uptake
v) If completely closed, it becomes a physiological tool for measuring gas and agent dynamics.

Disadvantages include:

i) It is the most complex system, with many components and thus bulky, heavy and expensive.
ii) Moisture may cause valves to stick (esp. the exhalation valve, or valves positioned near the patient), resulting in re-breathing.
iii) There is increased resistance to breathing.
iv) Potential for leaks, which is important if low flows are used.
v) Exhaustion of soda-lime is not always easy to detect.
vi) Cross infection may occur. The original systems were non-disposable and difficult to sterilise. Disposable systems are now readily available. Soda-lime is, however, a very hostile environment for bacteria and viruses. **Disposable** bacterial / viral filters may be used.

vii) Low flow anaesthesia may result in the accumulation of other gases that may be clinically important e.g. Methane, Acetone, Carbon Monoxide, etc.

viii) Trichlorethylene, Sevoflurane and Desflurane form toxic products with soda-lime. Trichlorethylene is seldom used nowadays and the Compound A of Sevoflurane has not been found in **clinically** important concentrations in normal use. Desflurane is associated with increased Carbon monoxide production if **dry** Baralyme (and possibly soda-lime) is used.

ix) Efficient CO_2 absorption results in hypocapnia, which can only be reversed by relative hypoventilation, and this may cause increased atelectasis.

x) Extra monitoring is required if very low flows are used, but these monitors are now considered a minimum standard for all anaesthesia, so this cannot be claimed as a disadvantage. Agent monitors are not essential, but desirable.

Although the Circle system can be used without a CO_2 absorber, this is illogical, as it will have none of the advantages of CO_2 absorption, will require a gas flow that exceeds those required by Mapleson-type systems and still have all the disadvantages of a Circle system.

Circle systems may be used with any fresh gas flow above the patient's basal requirements and may be classified as follows:-

BASAL- Flow	=	$1 \times \dot{V}_{O_2}$	» ± 218 mL min^{-1} (70 kg, 36,6 ° C, spontaneous breathing)
MINIMAL-	=	$1 - 2{,}5 \times \dot{V}_{O_2}$	» ± 218 - 550 mL min^{-1}
LOW-	=	$2{,}5 - 6 \times \dot{V}_{O_2}$	» ± 0,55 - 1,3 L min^{-1}
MODERATE-	=	$6 - 15 \times \dot{V}_{O_2}$	» ± 1,3 - 3,25 L min^{-1}
HIGH-	=	$> 15 \times \dot{V}_{O_2}$	» > 3,25 L min^{-1}

Low-flow anaesthesia is a topic in it's own right and will not be covered here.

CONCLUSION

Three types of Anaesthesia Breathing systems are in regular use, with which you should be familiar:-

a) Efferent Reservoir (ER) systems - e.g. the T-piece, Bain's
b) Afferent Reservoir systems, both Simple (SAR) - e.g. Magill, Lack
and (but much less so) Displacement (DAR) - e.g. E-AR, E-EAR
c) Circle CO_2 absorption system - Now the dominant system in regular use

Each system has its strong and weak points:-

ER Efficient for controlled ventilation, Inefficient for spontaneous ventilation
SAR Very Inefficient for controlled ventilation, Very Efficient for spontaneous ventilation
DAR Very Efficient for both controlled and spontaneous ventilation
Circle Most Efficient for controlled ventilation and Reasonable for spontaneous ventilation

Minimum fresh gas flow requirements are summarised as follows:-

Ventilation Mode Þ **Anaesthesia system** **ß**	**Spontaneous**	**Controlled**
Efferent Reservoir	$2 \times \dot{V}_E$	$1 \times \dot{V}_E$
Simple Afferent Reservoir	$0{,}7 \times \dot{V}_E$	$2 \times \dot{V}_E$
Displacement Afferent Reservoir	$0{,}7 \times \dot{V}_E$	$0{,}7 \times \dot{V}_E$
Circle CO_2 Absorption	≥ Basal $\dot{V}_{O_2}$	≥ Basal $\dot{V}_{O_2}$

The ideal Universal Anaesthesia Breathing system does not yet exist.
In the interim, we need to know the shortcomings and strong points of each breathing system that we may meet up with, and be capable of using these with safety and insight.

Scavenging of Anaesthesia Gases

INTRODUCTION

Anaesthesia gases and volatile agents are now considered to be a “substance hazardous to health” in many countries. This applies to long-term exposure to healthcare workers or allied personnel, not to the short-term exposure that patients are exposed to in clinical practice.

Human studies in the mid 1970's revealed that the cognitive and motor skills of volunteers were affected by exposure to concentrations of anaesthesia gas mixtures commonly found in unscavenged operating rooms. The results were not overwhelming, but there was enough to be a cause for concern. Animal studies using high concentrations (well beyond normal clinical concentrations) of nitrous oxide (N_2O) and / or halogenated agents did reveal a consistent increase in spontaneous abortions and foetal abnormalities after prolonged exposure.

Other *weak* associations that have been reported over the years include adverse neurological effects; reproductive risk to exposed female workers (increased early spontaneous abortions); developmental anomalies in their offspring; more daughters than sons born to male workers, and the possibility of liver disease (Halothane). No causal relationship to anaesthesia has been proven and similar effects are seen with other high stress occupations, e.g. airline pilots.

Permitted maxima in ppm as an 8 hour TWA		
Substance	**UK**	**USA**
N_20	100	25
Isoflurane	50	2
Enflurane	50	2
Halothane	10	2

Sevoflurane and Desflurane have yet to be given limits but 50 ppm is recommended.

Table 3 *Prescribed maximum levels for anaesthesia gases*
(TWA = time weighted average, ppm = parts per million)

The last 50 years has seen the introduction and many improvements in the management and control of anaesthesia waste gas. These include the routine mounting of an Anaesthetic Gas Scavenging System (AGSS) installation on anaesthesia workstations, more effective operating theatre ventilation systems and the increased adoption of low-flow techniques with minimal leaks.

Gas scavenging systems are the first line of defence and the preferred method of control to protect employees from exposure to anaesthetic gases, but theatre ventilation and anaesthesia techniques are equally important.

ANAESTHESIA SCAVENGING SYSTEMS

Most Anaesthesia Breathing Systems have an Adjustable Pessure-Limiting (APL) or "pop-off" valve for venting excess gas. Modern APL valves (cf. the old Heidbrink valve) are shrouded and fitted with a dedicated exhaust fitting for the AGSS system. The ISO standard connection is 30 mm, but 19 mm is also used; 22 mm and 15 mm (i.e. standard adult and paediatric connectors) should not be used to avoid incorrect connections of breathing systems.

Exhaust gases from the breathing circuit are processed by the AGSS system. Exhaust gas from side-stream gas analysers / capnographs, if not returned to the breathing system (as in low-flow anaesthesia), should also be scavenged.

An AGSS scavenging system normally consists of five basic components:

e) A gas collection assembly, e.g. a manifold collecting excess anaesthesia gas at the site of emission for delivery to the transfer tubing. Usually a 30 mm connection to the APL valve.
f) Transfer tubing conveying excess anaesthesia gas to the interface. Ideally 30 mm, but standard 22 mm breathing tubes are most often used.
g) The interface, which has a reservoir (bag, canister or wide-bore tube) capacity and provides positive (and preferably negative as well) pressure relief. It is designed to protect the breathing system from excessive positive (or negative) scavenging system pressure.
h) Disposal tubing conveying waste anaesthesia gas from the interface to the gas disposal facility.

i) The gas disposal facility, conveying the excess gases to a point where they are safely discharged to the atmosphere. Several methods in use include a non-recirculating ventilation system, the central vacuum system, a dedicated (single-purpose) waste gas exhaust system or a passive duct system. These may be combined with an absorber.

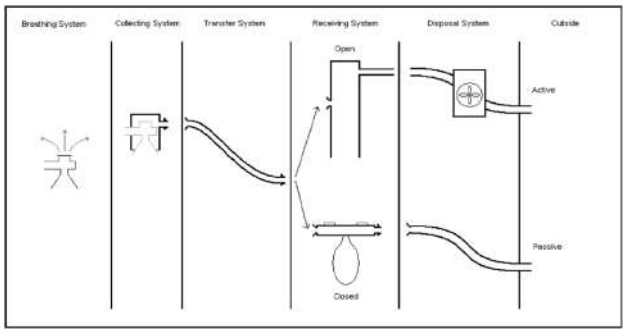
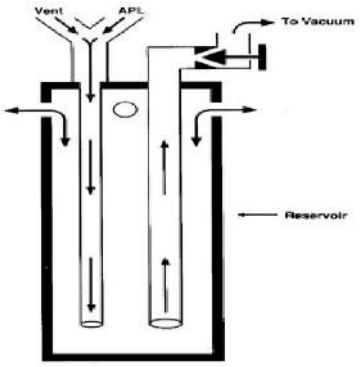


Fig 11 *Components of a scavenging system*

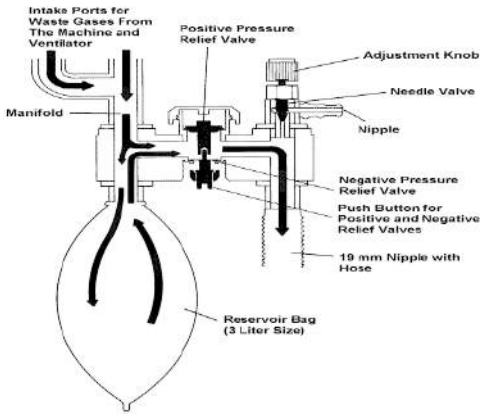
Mackenzie M. Anaesthetic Gas Scavenging
Update in Anaesthesia - http://www.worldanaesthesia.org

Anaesthesia workstations / machines have a machine-specific interface that must be integrated with the operating theatre's system for gas removal. The interface permits excess gas to be collected in a reservoir (bag, canister or tube) and limits the pressure (positive or negative) that can be transmitted to the breathing system. The collecting, transfer and interface components are often integrated inside a modern anaesthesia workstation, with only the disposal tube visible.
The gas disposal facility receives waste anaesthetic gases from the interface and should vent the waste gases outside the building; away from any air duct inlets or open windows, preventing the return of the waste gases back into the building.

The scavenging system at the interface may be *closed* or *open*:
Closed - The reservoir (may be a rigid container or a bag) is isolated from the atmosphere.
Open - The reservoir (usually a rigid container or large tube) is open to atmosphere



Open systems are always used with an active scavenger. Typically consist of a rigid reservoir (open to the ambient air) in which the gases are collected and a continuous suction applied for extraction.
These are simple and effective, but need a continuous source of suction. Failure of this suction will result in theatre pollution. Negative pressure is not conducted to the breathing system if there is no obstruction to ambient air ingress. Most modern anaesthesia workstations utilise this system.



Closed systems often have a bag as the reservoir and incorporate a positive pressure relief valve. These are usually active systems, but may be passive. Active systems have a negative pressure relief valve to prevent a negative pressure in the breathing system.
More complex, but if suction fails, it converts to a passive system and will still vent to atmosphere outside the operating theatre (assuming a low resistance to prevent opening the positive pressure relief valve). Relief valves must be checked!
Many older workstations (e.g. Ohmeda Modulus) had these systems.

Fig 12 *Open and Closed Anaesthesia Gas Scavenging Systems*

Dosch MP, Darin D
http://healthprofessions.udmercy.edu/programs/crna/agm/

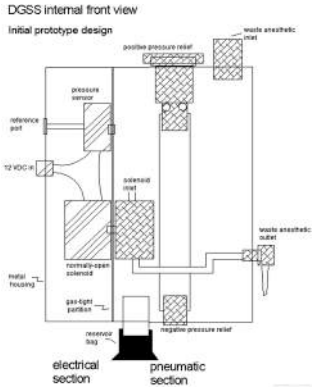
Scavenging may be accomplished by either a *passive* or an *active* process:

Passive - No vacuum or negative pressure is used.
Active - A vacuum or source of negative pressure is connected to the scavenging interface.

Active systems have a continuous negative pressure in the gas disposal tubing; whilst with a passive system, pressure will increase above atmospheric (positive) by the patient exhaling passively.

Active scavenging requires a *high-volume minimal negative pressure* supply, and dedicated theatre scavenging systems are designed to provide this. They have a separate and distinct wall probe. The central vacuum system (for clinical use) has a *low-volume potent negative pressure* (- 40 hPa) and requires conversion to a high-volume minimal negative pressure with flow restrictors and ambient air entrainment. The open system is imminently suitable for this and is the scavenging device seen in many of our operating theatres where the central (clinical) vacuum is used for scavenging.

If this is the system in use, then the vacuum pipe to the anaesthesia workstation must be plugged in at all times, even if there is another source of patient suction not attached to the machine.



The need for a continuous vacuum for active scavenging requires significant power to drive the vacuum pump. Dynamic AGGS (DGSS) uses an electronic device with sensitive negative and positive pressure sensors that control the vacuum and limits the vacuum power consumed.
Typically used in an active closed system with a bag as reservoir.

Fig 13 *A Dynamic Anaesthesia Gas Scavenging System*

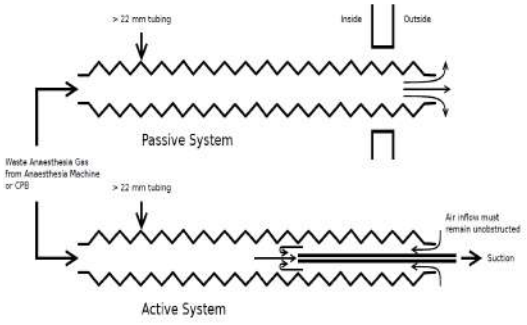
Barwise JA; Lancaster LJ; Michaels; Pope JE; Berry JM.
Anesthesia & Analgesia113(5):1064-1067, November 2011.

Other means of extraction include the use of circulating fans

Passive systems vent waste anaesthesia gas via the exhaust grille / duct of a non-recirculating ventilation system, or directly outside through a grille or window. This requires a large-bore tube with low resistance and as short as possible. The waste anaesthesia gas is moved along by the positive pressure from the breathing circuit until it reaches the gas disposal facility.

Despite the presence of an AGSS, occupational exposure to waste gases may still occur, particularly in paediatric anaesthesia with the use of valveless breathing systems (e.g. Jackson-Rees or Ayre's T-piece), inhalational induction and uncuffed endotracheal tubes. Other causes of occupational exposure are from the exhaled breath of patients recovering from inhalational anaesthesia (recovery area), filling of vaporisers, leaks in the breathing systems or the AGSS itself, poorly fitting facemasks or a sub-optimal placement of a LMA, etc. Perfusionists often utilise volatile agents during Cardio-Pulmonary Bypass for cardiac surgery and these are often not scavenged and a potent source of pollution - easily remedied by using a length of large-bore tubing and suction (see below).

Resource-poor solution:



The simplest passive scavenger is a large-bore tube attached to the breathing system and led outside (window, door, tent-flap). If continuous suction is available, this can be converted to an active scavenger by inserting a standard suction tube a good way in the open end and connect to the suction. Suction tube must not occlude the large-bore tube opening (< ⅓ of the diameter). The large-bore scavenging tube acts as a reservoir, but if it sucks the breathing system flat, reduce the suction power.

Fig 14 *A simple Passive or Active scavenger*

ABSORBERS

The absorption of anaesthesia volatile agents with activated charcoal is not a new development (the Cardiff Aldasorber has been available for many decades), but attracting renewed interest as a means of reducing their greenhouse and ozone effects on the atmosphere. Human anaesthesia has not embraced absorption to any large extent (it was utilised in the completely closed Dräger Physioflex), but is widely used in veterinary anaesthesia where high-flow techniques are still prevalent.

Activated charcoal will absorb all the anaesthesia volatile agents, but ***not nitrous oxide***. Saturation of the absorber is determined by weight, and when saturated could be heated in a safe area, the agents released and charcoal regenerated.

The AnaConDa acts as a charcoal filter for conserving anaesthesia agents. It is placed on the ETT (it's also an HME and filter). Not strictly a scavenger, but reduces personnel exposure.

Fig 15 *The AnaConDa (Anaesthesia Conserving Device)*

Reclamation and recycling of volatile anaesthesia agents is a new development and some companies in the UK, USA and Canada offer this service.
An activated charcoal canister is placed between the collection point on the breathing system and the AGSS. When saturated, the canisters are processed on-site and the volatile agents extracted as a liquid (containing a mixture of agents). This liquid is then purified at a central facility into their respective agents and may be re-used

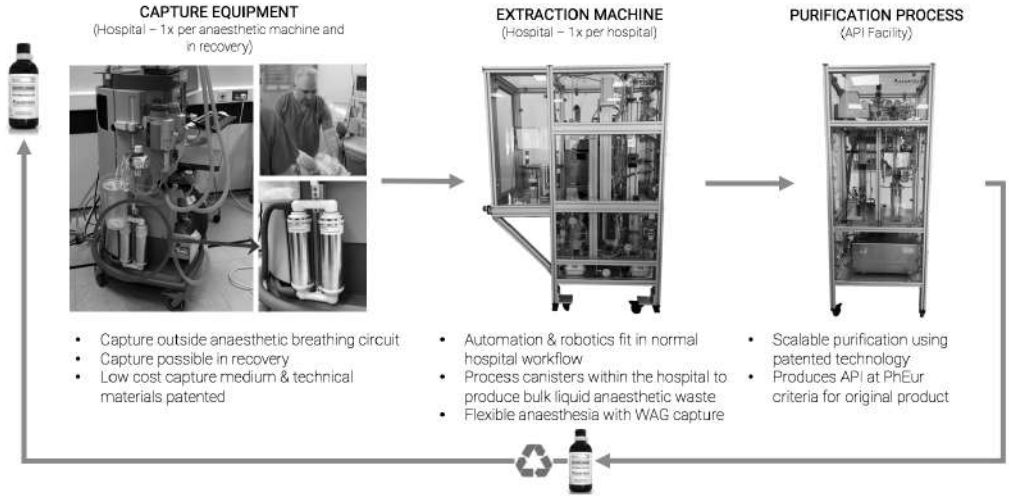


Fig 16 *Recycling volatile anaesthesia agents. N_2O is not absorbed*

Whether this process will be cost-effective remains to be seen, but it will minimise the greenhouse effect from the anaesthesia agents, but not N_2O.

CONCLUSION

Scavenging of waste anaesthesia gases is now routine and a standard of care. Although the evidence for actual harm from long-term exposure is not convincing, it is simple and relatively inexpensive to minimise this exposure.

As important as the AGSS, is the operating theatre ventilation system and this should supply at least 15 air exchanges per hour and be of the non-recirculating type.

Anaesthesia techniques also play a role, with low-flow techniques using a circle system causing less exposure and intravenous anaesthesia (TIVA or TCI) eliminating it altogether.

Paediatric anaesthesia remains the challenge.

Reclamation of anaesthesia agents with absorbers may well become a standard of care in the future.

Notes

BeneVision N

Always in Sight, Always in Mind

- Balance of Anaesthesia (BOA) for Induction, Maintenance and Recovery phases

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Uterotonic and Tocolytic Drugs
Pharmacology and relevant physiology

Dr Adalbert Ernst

Dept of Anaesthesia & Perioperative Medicine
University of Cape Town

Physiology of Uterine Contraction

During pregnancy, the number of oxytocin receptors in the myometrium and the decidua (pregnant endometrium) increases by a factor of 100, reaching a peak during early labour. This is mediated by oestrogen and may also be stimulated by uterine distention in late pregnancy.

In normal labour, uterine contractions are initiated by the binding of oxytocin released from the posterior pituitary) to the G-protein coupled oxytocin receptors in the myometrium. Via intracellular DAG and IP_3, calcium release triggers membrane depolarisation and contraction of myometrial smooth muscle.

At vaginal delivery, active management of the third stage of labour (the interval from delivery of the infant to expulsion of the placenta) is recommended. The major complications of the third stage of labour are haemorrhage (which may be from uterine atony), retained placenta, and uterine inversion.

At Caesarean section, uterotonic drugs are standard treatment after delivery of the infant and placenta to minimise the risk of uterine atony and postpartum haemorrhage.

UTEROTONIC DRUGS

General Principles

In modern practice, drugs that stimulate uterine contraction may be used

(1) To induce labour
(2) To augment existing labour
(3) After vaginal birth to facilitate uterine contraction and prevent post-partum haemorrhage
(4) At Caesarean section, following delivery of the fetus, to facilitate uterine contraction and prevent postpartum haemorrhage
(5) For the management of atonic uterus post-delivery
(6) For the management of active post-partum haemorrhage

A 2020 meta-analysis from the Cochrane Database concludes that oxytocin should be used as first-line treatment for PPH. The addition of misoprostol was found to have little to no difference to outcomes and was associated with side-effects. There was no evidence found for first line use of injectable prostaglandins, ergometrine, and Syntometrine®.

Specific Agents

Oxytocin and Analogues

Synthetic Oxytocin

This is the synthetic cyclic peptide form of the naturally occurring posterior pituitary hormone. Oxytocin remains the first-line uterotonic after both vaginal and Caesarean delivery, and is listed as part of the WHO Essential Drug List.

Chief Effects

Oxytocin stimulates uterine contraction in the following ways:

(1) Direct action: the hormone binds to oxytocin receptors in the myometrium, stimulating contraction of this uterine smooth muscle by increasing the sodium permeability of its myofibrils.

(2) It also increases intracellular calcium concentrations via the phospholipase C / IP_3 pathway.

(3) Oxytocin stimulates the formation of prostaglandins in the decidua, which enhance the oxytocin-induced contractions.

Oxytocin administration results in a dose-related increase in both the amplitude and frequency of uterine contractions. If given by slow intravenous infusion to induce labour, oxytocin causes regular coordinated contractions that travel from fundus to cervix.

The effective dose (ED) of synthetic oxytocin is small—the ED(90) was found to be 0.29 IU/min (amounting to 15IU of oxytocin in 1L of intravenous fluid over a one-hour period in a 2010 study. The minimum effective bolus dose may be as low as 0.3 units.

Other effects

(1) Oxytocin contracts myoepithelial cells in the mammary gland, causing milk let-down (expression of milk from alveoli and ducts).

(2) Vasodilator action, which is more pronounced with higher dosage and faster injection. The drop in blood pressure typically results in a reflex tachycardia. Flushing and dizziness are common if the drug is given rapidly.

(3) As oxytocin is structurally similar to vasopressin, it has a weak antidiuretic action which can become clinically significant with high doses, repeated infusions, and administration of high volumes of intravenous fluids. Frank water retention and hyponatraemia may occur in these cases.

Presentation is usually in ampoules of 10IU or 5IU per mL. For IV use it is normally diluted to 1 IU/mL. It is heat-labile and light-sensitive, and must be stored between 2–8 ºC in a fridge.

Pharmacokinetics

Intravenous oxytocin has an almost immediate action, with peak concentration after 30 minutes Intramuscular oxytocin has slower onset of action, lasting 3–7 minutes, but results in a longer lasting clinical effect of up to 1 hour.

Half-life: 1–6 minutes. It is inactivated in the liver and kidneys and is also destroyed by circulating placental oxytocinase.

Dosage

IV bolus of oxytocin is common, but care should be given to use the lowest dose necessary and to deliver the bolus slowly (typically 3 units or less over 1-3 minutes). Rapid injections of high doses have led to cardiovascular collapse and even death in women undergoing Caesarean delivery under neuraxial anaesthesia.

Following bolus injection, initiation of an oxytocin infusion is common. The dosage of oxytocin infusion used for prevention of PPH varies significantly from institution to institution. A commonly used dose is 10 to 40 international units of oxytocin in 500 to 1000 mL of suitable isotonic crystalloid, with the rate of infusion adjusted according to uterine tone, up to 500 mL/hour. The rate is then decreased (e.g., 1 to 2.5 international units/hour) as long as uterine tone is maintained and bleeding is not excessive. Although the total infusion time in patients with normal uterine tone and volume of bleeding is variable, a minimum of four hours after birth is common

Carbetocin

This is a long-acting synthetic analogue of oxytocin with the usual agonist properties. It binds to oxytocin receptors in the uterine smooth muscle, resulting in rhythmic contractions, increased frequency of existing contractions, and increased uterine tone.

It is available as a heat-stable formulation in single-dose ampoules of 100 µg/mL.

Pharmacokinetics

Intravenous carbetocin results in sustained uterine contractions within two minutes. These last for about six minutes and followed by rhythmic contractions for 60 minutes. It should be administered as a slow bolus (typically over 1 minute).

Given intramuscularly, sustained uterine contractions will last for about 11 minutes and rhythmic contractions for 120 minutes. It has a half-life of 40 minutes. The IM route is recommended only for vaginal delivery.

Ergometrine

Ergot (*Claviceps purpurea*) is a fungus that grows on rye which contains several pharmacologically active substances. One of these, ergometrine, was isolated in 1935 and was recognised as a uterotonic agent.

Ergometrine and its semisynthetic analogue methylergometrine increase uterine muscle tone by causing sustained uterine contractions. The action depends partly on the contractile state of the organ: ergometrine has relatively little effect on a normally-contracted uterus post-delivery, but can initiate strong contractions if the uterus is inappropriately relaxed.

Its mechanism of action is poorly understood but is thought to bind to alpha adrenergic receptors on the myometrial cell and alter transmembrane calcium channel activity, resulting in calcium influx. It may also work via 5-HT receptors.

Other effects

- Nausea and vomiting are common, possibly via stimulating dopamine. D_2 receptors in the chemoreceptor trigger zone
- Vasoconstriction with an increase in blood pressure and associated blurred vision and headache
- Frank vasospasm of the coronary arteries may occur, resulting in angina

As such the use of ergometrine is contra-indicated in patients with hypertension, migraines, and ischaemic heart disease.

Pharmacokinetics

IM: onset of action within 2–3 minutes, lasting for about 3 hours. A typical IM dose is 0.2 mg

IV: onset of action within one minute, lasting 45 minutes (although rhythmic contractions may persist for up to three hours)
Half-life: 30–120 minutes

Like synthetic oxytocin, ergometrine needs to be protected from light and requires refrigeration between 2–8 ºC. Presentation is typically in ampoules of 0.2 or 0.5mg, this is usually diluted to 0.1 mg/mL.

Combined Oxytocin and Ergometrine (Syntometrine®)

This is a fixed drug combination consisting of 5IU of oxytocin and 0.5 mg of ergometrine in 1 mL of the undiluted ampoule.

Given intramuscularly, the latent period for uterine response is about 2.5 minutes, and the uterotonic effects last for around three hours.

If used intravenously, it should be diluted to a concentration of 1IU:0.1mg/mL.

Prostaglandins

The endometrium and myometrium have substantial prostaglandin-synthesising capacity. Prostaglandin $F_{2\alpha}$ is produced in large amounts and, in the non-pregnant uterus, and is implicated in physiologic ischaemic necrosis of the endometrium that precedes normal menstruation. The uterus also produces vasodilatory prostaglandins (PGE_2 and PGI_2/prostacyclin).

Both the E and F series prostaglandins cause uterine contraction. The sensitivity of uterine muscle to prostaglandins increases during gestation. PGE_2 and $PGF_{2\alpha}$ cause co-ordinated contractions of the body of the pregnant uterus while relaxing the cervix. Both series will reliably terminate pregnancy in the first and second trimesters, as opposed to oxytocin, which does not cause expulsion of uterine contents in these stages.

Prostaglandins cause uterine contractions by altering membrane permeability and increasing the intracellular calcium signal. They promote the formation of gap junctions, facilitating transmission of signals throughout the myometrium. They also upregulate the expression of oxytocin receptors in the uterus, which in turn promotes contractility.

The prostaglandins used in obstetrics comprise misoprostol, dinoprostone, and carboprost which are analogues of prostaglandins E_1, E_2, $F_{2\alpha}$ respectively.

Dinoprostone and Carboprost are sometimes termed “injectable” prostaglandins, but should never be given intravenously because of the high risk of severe adverse effects.

Misoprostol (Cytotec®)

Misoprostol is a synthetic analogue of natural prostaglandin E1 and is available as tablets (200 µg and 25µg are listed in the WHO Essential Medicines list). The tablets may be given either orally, rectally, or vaginally.

It has oxytocic properties, inhibits gastric acid and pepsin secretion, and enhances gastric mucosal resistance to injury

Pharmacokinetics
Absorbed 9–15 minutes after sublingual, oral, vaginal or rectal use

Oral and sublingual routes have the advantage of rapid onset of action, while the vaginal and rectal routes result in prolonged activity and greater bioavailability

Half-life: 20–40 minutes

Common side-effects of misoprostol include shivering and fever. Pyrexia is usually preceded by shivering and peaks at 1-2 hours and then declines over three hours spontaneously. Other side-effects include vomiting and diarrhoea (reported incidence of 5%).

Dinoprost (Prostaglandin E_2)

Dinoprostil is available as an endocervical gel (Prepidil®), oral tablet, and suppository. It may be used for cervical ripening to induce labour, and has also been used for termination of intrauterine pregnancy.

Adverse effects are rare with the topical preparations.

Carboprost (Hemabate ®, Prostaglandin $F_{2\alpha}$)

Carboprost may be considered for refractory postpartum uterine bleeding or uterine atonia.

For atonia at Caesarean section, direct surgical infiltration of the uterus (typically in 4 quadrants) can be considered. Alternatively, some centres use intramuscular carboprost. The drug should never be given intravenously.

Adverse reactions are numerous and potentially fatal. The effects are mainly due to smooth muscle contraction. Cardiovascular side-effects include chest pain, hypertension, palpitations, tachycardia and syncope. Respiratory side-effects of significance include bronchospasm (which may be severe)

TOCOLYTIC DRUGS

General Principles and Indications

Administration of tocolytic drugs can reduce the strength and frequency of uterine contractions. In women with acute preterm labour, a 2009 meta-analysis of randomized trials found that these drugs were more effective than placebo/control for delaying delivery for 48 hours and for seven days, but not for delaying delivery to 37 weeks. Furthermore, women treated with tocolytics did not achieve statistically significant reductions in important newborn clinical outcomes, such as respiratory distress and survival.

Given the limited ability of tocolytic therapy to delay delivery for a prolonged period of time, the major goals of treatment of acute preterm labour are to:

- Delay delivery by at least 48 hours (when safe to do so) so that antenatal corticosteroids administered to the mother have time to achieve their maximum fetal/neonatal effects. Pre-delivery administration of betamethasone reduces the risk of neonatal death, respiratory distress syndrome, intraventricular haemorrhage, and necrotizing enterocolitis in preterm neonates.
- Provide time for safe transport of the mother, if indicated, to a facility that has an appropriate level of neonatal care if she delivers preterm.
- Prolong pregnancy (when safe to do so) when underlying, self-limited conditions that can cause labour, such as pyelonephritis or abdominal surgery, are present but unlikely to cause recurrent preterm labour.

In addition, many providers administer tocolytics to women with recurrent preterm labour before 34 weeks in an attempt to prolong gestation, even when another course of corticosteroid therapy and/or maternal transfer is unnecessary. The value of this approach has not been studied in a randomized trial.

Choice of agents

For most women at 24 to 32 weeks of gestation who are candidates for tocolysis, indomethacin is typically used as first-line therapy due to its favourable maternal and fetal side effect profile. It should not be used for more than 72 hours because of concern about premature constriction of the ductus arteriosus and oligohydramnios. If indomethacin is contra-indicated, nifedipine may be used as a first-line agent

For women at 32 to 34 weeks of gestation, nifedipine is preferred, owing to conkers about adverse fetal effects.

Beta-2-agonists are now considered second-line agents.

Specific Agents

Prostaglandin Inhibitors (Cyclooxygenase inhibitors)

Cyclooxygenase inhibitors are commonly used in obstetrics for acute tocolysis and as an intervention for preterm cervical shortening. COX inhibitors prevent the conversion of arachidonic acid to prostaglandin. Prostaglandins have a significant role in the labour process by stimulating myometrial gap junction formation and by increasing the intracellular calcium level. Thus, COX inhibitors work to inhibit labour through the prevention of prostaglandin formation. COX inhibitors in use for tocolysis are non-specific; there is limited information on the use of COX-2 specific agents.

Indomethacin

Indomethacin is the most common COX inhibitor used for tocolysis. It is typically administered as a loading dose of 50–100 mg orally or rectally, followed by 25 mg orally every 4–6 hours .Oral indomethacin is rapidly absorbed and distributed systemically in the plasma with 99% being protein bound .The half-life of the medication is approximately 4.5 hours. It is eliminated via metabolism, renal and biliary excretion.

Long-term indomethacin use requires close fetal surveillance. Indomethacin can cause premature closure of the fetal ductus arteriosus and oligohydramnios. Neither of these complications has been reported in the setting of short-term tocolysis (≤48 hours) prior to 34 weeks' gestation; however, they have been reported with long-term use.

Premature narrowing or closure of the ductus arteriosus can lead to pulmonary hypertension in the newborn and fetal and neonatal tricuspid regurgitation from increased right ventricle afterload.

Maternal side effects, including nausea, oesophageal reflux, gastritis, and emesis, are seen in approximately 4 percent of women treated with indomethacin for preterm labour. Platelet dysfunction may occur. Alterations in maternal cardiovascular physiology are minimal.
Gastrointestinal upset is a common maternal side effect of indomethacin.

Calcium channel blockers

The calcium channel blockers are commonly used as first-line agents for acute tocolysis.

They relax smooth muscle in two ways

- Blocking the entry of calcium ions into the myometrial cell directly
- Prevention of intracellular calcium release from the sarcoplasmic reticulum

Since calcium is required for the phosphorylation of myosin light-chain kinase (MLCK), in its absence, MLCK is inactivated, causing uterine relaxation.

Nifedipine

Nifedipine is the most commonly used drug of this class for acute tocolysis. The relative safety, maternal tolerance, ease of administration, and reduction in adverse neonatal outcomes support use of nifedipine rather than beta-agonists for inhibition of acute preterm labour.

Common maternal side-effects include hypotension, flushing, nausea, headache, dizziness and anxiety. Coughing and frank dyspnoea have also been reported. In women with no underlying myocardial dysfunction, compensatory changes (reflex increase in heart rate and stroke volume) generally maintain blood pressure and cardiac output. Nifedipine should be used with caution in women with heart failure and a reduced ejection fraction.

Nifedipine appears to have minimal fetal side-effects at the doses currently used.

Beta-2 agonists

β-Adrenergic-receptor agonists bind β2-adrenergic receptors on the myometrial cell. This interaction leads to increased cAMP and activation of protein kinase. Protein kinase inactivates MLCK and prevents contraction. The beta-2-agonists ritodrine and terbutaline have been studied in several randomized, placebo-controlled trials. Salbutamol and hexoprenaline have also been evaluated, but data are sparse. Although ritodrine is the only drug approved by the US Food and Drug Administration (FDA) for the treatment of preterm labour, it is no longer available in the United States.

Currently, this class of drugs is only used as second-line agents when first-line agents have failed or are contra-indicated.

Maternal side effects are related to stimulation of beta-1 adrenergic receptors, which increase maternal heart rate and stroke volume, and stimulation of beta-2-adrenergic receptors, which causes peripheral vasodilation, diastolic hypotension, and bronchial relaxation. The combination of these two cardiovascular effects leads to tachycardia, palpitations, and lower blood pressure.

Beta-agonists cross the placenta. Fetal effects, such as fetal tachycardia, are analogous to the maternal effects noted above. Neonatal hypoglycaemia may result from fetal hyperinsulinemia in response to prolonged maternal hyperglycaemia. Fetal acid/base status and neonatal well-being are not compromised by these agents.

Data are too limited to support the use of any particular beta-agonist over another. In the United States, terbutaline is the most commonly used beta-agonist for labour inhibition and has a preferential effect on beta-2-adrenergic receptors. It is often given subcutaneously by intermittent injection. The dose is variable: 0.25 mg can be administered subcutaneously every 20 to 30 minutes for up to four doses or until tocolysis is achieved. Once labour is inhibited, 0.25 mg can be administered subcutaneously every three to four hours until the uterus is quiescent for 24 hours.
Terbutaline and salbutamol can also be administered as a continuous intravenous infusion.

$MgSO_4$

Magnesium sulphate has been used as a tocolytic since the 1960s. Magnesium acts via both extra- and intracellular pathways to decrease intracellular calcium concentrations, thereby preventing contraction. However, meta-analysis has shown that it is no better than placebo for preventing pre-term delivery, so it is mentioned here for completeness' sake only. Doses used in the literature are typically 6 grams as a loading dose over 20-30 minutes, followed by a continuous infusion of 2g/hour.

Oxytocin Receptor Blockers

Atosiban is a selective oxytocin-vasopressin receptor antagonist that competitively inhibits oxytocin from binding to its receptors in the myometrium and decidua. It does not yet have FDA approval in the USA, but is used in Europe for acute tocolysis.

Nitric oxide donors

Nitric oxide is a potent vasodilator and smooth muscle relaxant produced by a variety of cells. Nitric oxide relaxes smooth muscle via interaction with guanylyl cyclase. This interaction increases guanosine monophosphate (cGMP), which in turn inactivates myosin light-chain kinase leading to smooth muscle relaxation.

Nitroglycerin (NG) is more commonly used for acute uterine relaxation in the setting of uterine inversion, or to facilitate external cephalic version, fetal delivery at the time of c-section, uterine relaxation for fetal surgery, and/or to relieve fetal head entrapment with vaginal breech delivery. It has been shown to be an effective uterine/cervical relaxant when administered at a dose of 100–200 mcg IV . The half-life of NG is very short at 1–4 minute . Common side effects include hypotension, flushing, and headache. One may encounter uterine atony after administration, thus, uterotonics should be readily available.

Nitroglycerin has been studied in randomized controlled trials as a tocolytic. Intravenous nitroglycerin was shown to be inferior to magnesium sulphate as a tocolytic [52] . Transdermal nitroglycerin was found to be superior to placebo and similar to ritodrine with respect to delaying delivery for 48 hours [5354] . Although nitroglycerin has been shown to delay delivery, its use as a tocolytic is limited secondary to the potential for significant maternal hypotension.

Volatile anaesthetic agents

All halogenated volatile anaesthetic agents, by virtue of being calcium channel blockers, relax smooth muscle, and as such, relax uterine muscle. Halothane appears to have the greatest effect. While this is usually considered a negative side-effect, volatile anaesthesia may be utilised to assist removal of a retained placenta.

For Caesarean section under general anaesthesia, it is recommended that the concentration of volatile be reduced to 0.75 MAC with additional nitrous oxide and appropriate opioids to maintain depth of anaesthesia.

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Notes

Antifibrinolytics

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In the past decade, targeting the fibrinolytic system has been an important pharmacological strategy for blood conservation in current medical practice. Antifibrinolytics have consistently shown to reduce and control bleeding in trauma patients developing clinical hyperfibrinolysis. It has also been an effective means to control bleeding during or after surgery, such as cardiac, orthopaedics, trauma, liver surgery and obstetrics. These agents can also help people with hereditary or acquired bleeding disorders and it has also been used as an established antidote for patients treated with thrombolytic agents that have experienced bleeding complications.

However, there is also evidence of complications associated with exaggerated thrombosis that should be weighed up against the benefit of using these drugs. The primary use of antifibrinolytics is to prevent fibrinolysis in other words the lysis of a blood clot or a thrombus.

Tranexamic acid specifically has become a major part of Patient Blood Management (PBM) world-wide as it forms part of protocols for blood conservation therapy. It's widely available, easy to administer and relatively inexpensive.

The fibrinolytic pathway

Fibrinolysis is initiated as part of the haemostatic response and regulates the extent of fibrin formation and vascular obstruction during haemostasis. This is considered a protective physiological response to limit clot formation. Following tissue and vascular injury, multiple haemostatic processes are initiated where thrombin is generated, platelet adhesion happens, and the cross-linking of platelets and fibrin takes place. Fibrin is the end product of coagulation activation and becomes a co-factor for plasminogen activation by tissue plasminogen activator.

During normal fibrinolysis, intravascular clots are dissolved when inactive circulating plasminogen binds to fibrin through an active site that binds lysine. This is a locally activated pathway where plasminogen is enzymatically processed to plasmin by plasminogen activators in the tissue such as t-PA and urokinase. Plasmin limits the growth of the clot and dissolves the fibrin network as wounds heal.

Plasminogen is the inactivated precursor that is converted to plasmin through cleavage of a single peptide bond. Plasmin is a non-specific protease, which digests not only fibrin clots but also certain plasma proteins including some coagulation factors. The fibrinolytic system will remove unwanted fibrin thrombi while fibrin in the wound persist to maintain haemostasis.

Inhibiting fibrinolysis may potentially also inhibit other processes that contribute to bleeding. Fibrinolysis can also cleave GP1b and IIIb/IIIa receptors on platelets reducing platelet adhesion and aggregation.

t-PA - Tissue plasminogen activator is released from vascular endothelial cells when there is trauma or stasis produced from vascular occlusion. It is cleared from the blood or inhibited by a circulating inhibitor, plasminogen activator inhibitor-1, and thus exerts little effect on circulating plasminogen. Plasminogen activator inhibitor-2 inhibits urokinase-plasminogen activator. Tissue plasminogen activator binds to fibrin and converts plasminogen to plasmin.

The molecular inhibitors of fibrinolysis include plasminogen activator inhibitor 1 that inhibits tissue plasminogen activator and plasminogen activator inhibitor 2 that inhibits urokinase-plasminogen activator 2. The physiologic inhibitor of plasmin is alpha-2-antiplasmin but currently called plasmin inhibitor. Also, α2-macroglobulin functions as a plasmin inhibitor. Factor XIIIa, a transglutaminase, cross-links fibrin to increase clot strength and render it more resistant to fibrinolysis.

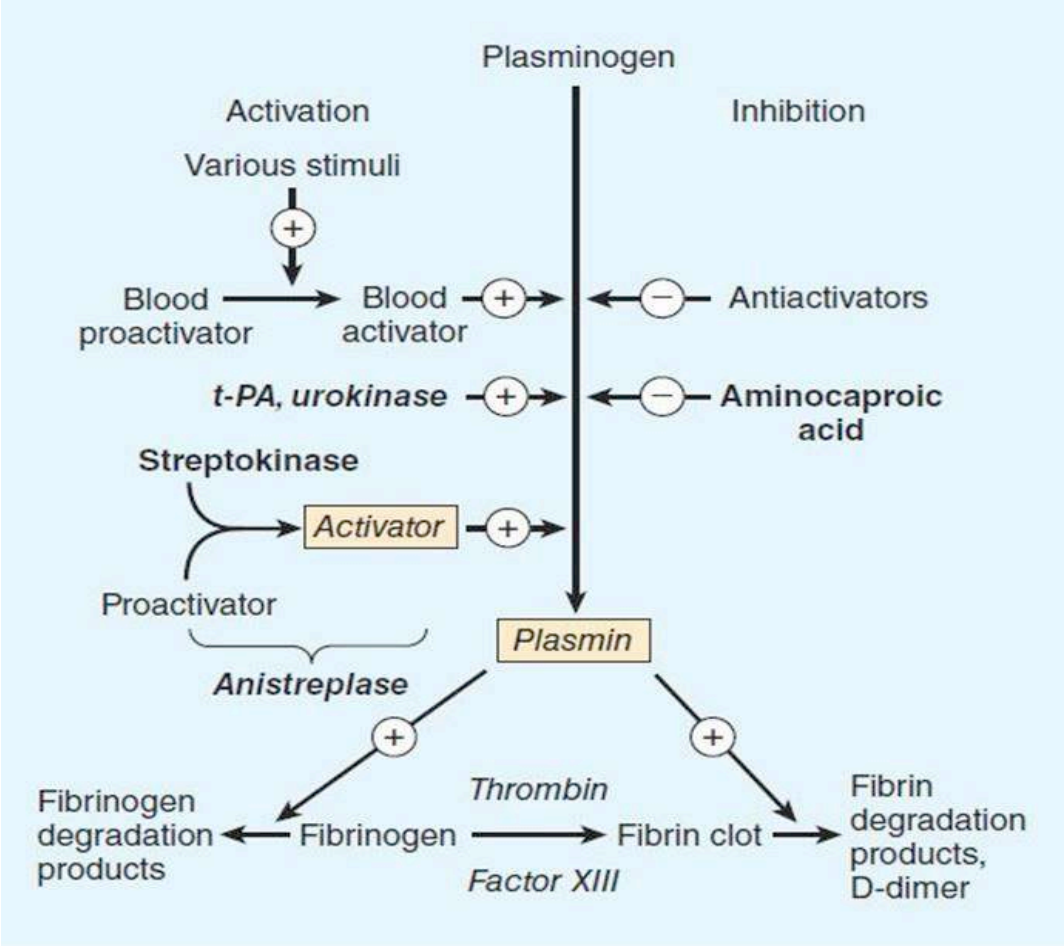

Figure 1: The fibrinolytic system

Pharmacology

Antifibrinolytics are categorised into two groups of which the first group, the lysine analogues (amino acids) mainly inhibit plasminogen to be activated to plasmin and the binding of plasmin to fibrinogen and fibrin. This prevents clots from breaking down.

The second group is the proteinase inhibitors, which inhibit plasmin and kallikrein, thereby preventing fibrinolysis. It also assists with haemostasis by protecting the platelet membrane adhesive receptor GP Ib.

I Amino acids (lysine analogues)

a) Epsilon aminocaproic acid (EACA)

b) Tranexamic acid

II Serine proteinase inhibitors

a) Aprotinin

I Amino acids (lysine analogues)

1. Mechanism of action of a) Epsilon aminocaproic acid and b) Tranexamic acid

Antifibrinolytics improve haemostasis through:

- inhibition of systemic fibrinolysis
- platelet preservation
- decreased release of tissue Plasminogen activator by inhibiting the formation of compounds which release tPA

Epsilon aminocaproic acid (EACA, 6-aminohexanoic acid, Amicar^{R}) and tranexamic acid (TXA, Cyclocapron^{R}) are structural analogues of lysine, which competitively bind to the lysine-binding sites on plasminogen and plasmin. This inhibits the binding of plasmin to fibrin and subsequently fibrinolysis.

Evidence suggests that tranexamic acid may also improve platelet function and inhibit plasmin induced platelet activation which facilitate clot stabilization rather than thrombogenesis.

Plasminogen and plasmin are also pro-inflammatory mediators in response to injury. They play a vital role in activation of the cellular and complement inflammatory response. Tranexamic acid may attenuate this inflammatory response during trauma, which contributes to the coagulopathy and also preserves the integrity of the glycocalyx. Unfortunately, this has only been shown in animal studies.

Antifibrinolytics stabilise clots by inhibiting the natural degradation of fibrin. The problem is that thrombi that are formed with the drug are not lysed.

2. Pharmacokinetics

The lysine-analogues can be given intravenously or orally. There are studies being conducted looking at the pharmacokinetics of TXA given intramuscularly as well.

Epsilon aminocaproic acid (EACA) is rapidly excreted in the urine and administration via intravenous infusion is necessary to maintain therapeutic plasma concentrations. The elimination half-life is 2 hours via glomerular filtration and it is excreted unchanged in the urine for up to 36 hours. A loading dose of 50mg/kg followed by a 25mg/kg/hr infusion has been suggested to inhibit the fibrinolytic system. This drug is most widely used in the United States where most other countries use TXA.

Tranexamic acid (TXA) administered to healthy individuals in a dose of 10mg/kg intravenously, is distributed through the intra- and extracellular compartments and demonstrates a peak plasma concentration at 60 minutes with a half-life of about 2 hours. Renal elimination via glomerular filtration is 30% in the first hour and 90% within 24 hours. An antifibrinolytic dose remains in the tissue for up to 17 hours and in the serum for up to 8 hours. It crosses the placenta and a small dose appears in breast milk. It rapidly appears in synovial fluid.

Oral administration of 10-15mg/kg causes a peak plasma concentration after 3 hours. To acquire a 98-100% reduction in fibrinolytic activity, a concentration of 100mg/L in the plasma is required. For patients with menorrhagia doses of 1.3g is given orally every 8 hours for up to 5 days.

TXA is 7-10 times more potent than EACA and has a more sustained antifibrinolytic activity in tissues.

The pharmacokinetics may differ in trauma patients and there are currently clinical trials being conducted to determine the pharmacokinetics of the effects of TXA on haemostasis and immune systems.

There is a large dose range described from 10mg/kg to a 10g bolus followed by a 0-2g/hour infusion of TXA. However, there is very little evidence to support a regime exceeding a bolus of 10mg/kg followed by an infusion of 1mg/kg.

3. Adverse events

The adverse events of EACA include hypotention, cardiac arrythmias, rhabdomyolysis and renal dysfunction.

Adverse events of tranexamic acid are rare and mainly limited to nausea, diarrhoea and abdominal pain. These symptoms are dose related and will disappear if the dose is reduced. The dose should also be reduced in patients with renal insufficiency to avoid accumulation and its associated adverse events. Hypotension can occur and is generally associated with a rapid infusion.

Tranexamic acid has less adverse events than aminocaproic acid due to the lower daily dose requirement. It has also occasionally been associated with bullous eruptions of the skin.

Tranexamic acid has also been associated with seizures, the risk of which is likely to be dose related. This is mostly evident in the post-operative period and possible mechanisms include neuronal excitation by antagonising GABA inhibition and glycine neurotransmission at receptor level. This can be attenuated by isofluorane and propofol. This effect has been extensively studied in cardiac surgery, which shows a higher incidence in seizures post operatively in patients receiving TXA compared to placebo. TXA appears to reduce blood loss and the need for transfusions but at the cost of seizures post-operatively. Risk for seizures are also higher in patients with renal insufficiency.

There is no evidence that TXA predispose patients to thrombosis but it may perpetuate existing fibrin deposits.

TXA should be stopped if any disturbances in colour vision occur and the dose should be reduced if there is any gastrointestinal upset such as nausea, vomiting or diarrhoea. The incidence is about 15%.

The risk of thrombosis

There has been a concern amongst clinicians about the potential hypercoagulable state when giving antifibrinolytics. There may be a prothrombotic effect of plasmin during therapeutic fibrinolysis, this is from plasmin-mediated prothrombin and platelet activation. However, despite concerns, thrombosis has not been a significant clinical complication. In major randomized controlled trials of antifibrinolytics in orthopeadic surgery and trauma, there were no increases in thrombotic complications compared to controls.

4. Uses

- These agents are used in the treatment of primary menorrhagia, epistaxis and oral bleeding with tooth extractions in patients with congenital and acquired coagulation disorders.
- Used for haemorrhagic complications associated with thrombolytic treatment.
- They reduce blood loss associated with different surgeries such as joint replacements, spine surgery, cardiac surgery and orthotopic liver transplants and obstetric surgery.
- As treatment when hyperfibrinolysis is demonstrated in acute trauma patients
- They are also given to patients with acute promyelocytic leukaemia (where high production of plasmin can cause life-threatening haemorrhage) and in liver transplantation (unlicensed).

Fibrinolysis is a key component of the coagulopathy post bypass, which makes antifibrinolytics a great option to decrease bleeding and lesson the need for allogeneic blood transfusions. The mechanism of action being via the inhibition of plasminogen activation and to a lesser degree via antiplasmin activity. It also decreases microvascular bleeding in the post-bypass period and prevents re-explorations for bleeding.

There is a mortality benefit using TXA in trauma patients that are bleeding, require massive transfusions or when hyperfibrinolysis is demonstrated. Increased activated protein C as a result of the body's response to traumatic injury, which is largely responsible for the acute traumatic coagulopathy, is a condition which is characterized by dysfibrinogenemia, hyperfibrinolysis, endothelial dysfunction

and impaired platelet activity. A secondary cause of coagulopathy is haemodilution, hypothermia and acidosis, which contribute to the haemostatic dysfunction.
Due to the results of the CRASH2 trial, TXA given to trauma patients showed a significantly lower mortality especially if giving within the first 3 hours after injury.

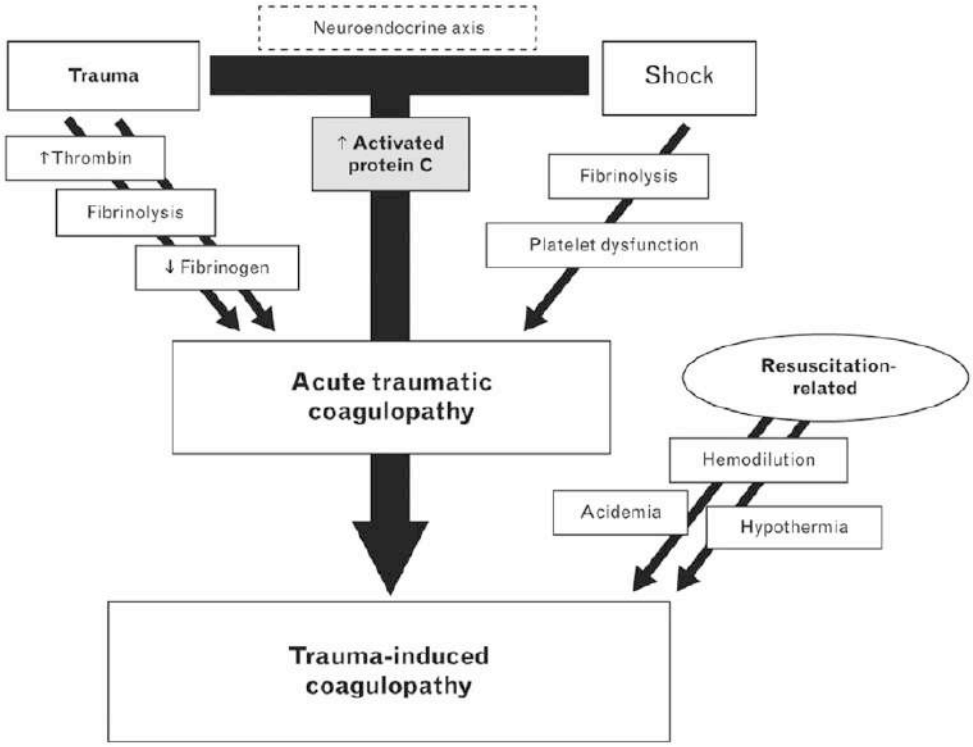

Figure 2 Acute trauma coagulopathy

Fibrinolysis is an important pathophysiological component of coagulopathy developing from trauma. Mortality in trauma patients is largely attributed to hyperfibrinolysis and it has been re-affirmed by many studies as part of the pathogenesis of Acute Traumatic Coagulopathy. However, it has been somewhat concerning that the general use of antifibrinolytics such as TXA shouldn't be given to all trauma patients, but only to those with hyperfibrinolysis. The World Maternal Antifibrinolytic (WOMAN) trial evaluated early administration of TXA on mortality, hysterectomy and post-partum haemorrhage and concluded that death due to bleeding was reduced in the TXA group compared to placebo with no difference in the adverse events. Patients with intracranial haemorrhage, ongoing bleeding or a secondary bleed is a major cause of morbidity and mortality. After subarachnoid haemorrhage, a recurrence of bleeding within 24hrs carries a mortality risk of 60% and antifibrinolytic therapy can reduce the bleeding, however the CRASH3 trial concluded that there was a trend towards a reduced mortality in the TXA group when given within 3 hours but it was not statistically significant.

5. Contra-indications

- Severe renal impairment
- Thromboembolic disease
- Massive haematuria – to avoid the risk of ureteric obstruction
- Disseminated intravascular coagulopathy
- Pregnancy
- Porphyria

6. Viscoelastic testing prior to administration of antifibrinolytics

Viscoelastic testing of coagulation includes the TEG and ROTEM tests and has been recommended by some investigators prior the administration of TXA because of some serious adverse events in a specific subset of patients. Others have argued that these tests are not sufficiently sensitive and the delay in administration while waiting for the results might negatively influence the patient. Trauma centres across the world are incorporating TXA with their Massive transfusion Protocols (MTP), however it still remains a challenge to predict who will need MT.

II Serine Proteinase inhibitors

Aprotonin

1. Mechanism of action

Aprotinin is a protease inhibitor, isolated from bovine lung. It combines reversibly to the active site of pancreas-secreted trypsin – a digestive enzyme. Pancreatic trypsin represents a large family of protein breaking enzymes called serine proteases and bovine anti-trypsin represents a family of anti-enzymes that inhibit serine proteases.

Aprotinin has a significant affinity for pancreatic trypsin and variable affinities for trypsin-like enzymes and forms reversible complexes at the serine components of certain enzymes. The trypsin-like enzymes include plasmin, plasminogen activator, kallikrein and thrombin, also activated clotting factors – 7,9,10, 11 and 12. Of these enzymes, kallikrein and plasmin are very sensitive to aprotinin inhibition and they play a key role in stimulating inflammation, coagulation, and fibrinolysis during and immediately after Cardiopulmonary bypass (CPB). The effect correlates in a dose-dependent manner – inhibiting plasma protease enzymes.

Kallikrein activity increases with CPB leading to neutrophil stimulation and increased production of bradykinin, which contribute to increased vascular permeability leading to tissue oedema, hypotension and hypoperfusion. Kallikrein activity is completely inhibited by full doses of aprotinin, and the haemostatic effect is primarily due to the inhibition of plasmin. This activity can be measured through the generation of D-dimer, a by-product of fibrinolysis. The antifibrinolytic effect of aprotinin is dose related and completely inhibiting D-dimer formation at the full dose, but not lower doses. Fibrin degradation products stimulates the inflammatory response and inhibits platelets, which means the effects of aprotinin are antifibrinolytic, anti-inflammatory and platelet sparing.

Thrombin activation depends on the proteolytic receptor protease-activated receptor 1 (PAR1). Aprotinin blocks PAR1 and therefore inhibits thrombin. Thrombin is a potent inducer of platelet aggregation and is also pro-inflammatory. Platelets however can still be activated through other mechanisms such as ADP, adrenaline and collagen, so aprotinin does not completely inhibit platelet aggregation.
Aprotinin inhibits pro-inflammatory complement factors, neutrophil activation, platelet aggregation and subsequent dysfunction and cytokine secretion.

- Inhibition of t-PA, preventing conversion of plasminogen to plasmin
- Inhibits fibrinolysis
- Inhibits kallikrein, plasma kallikrein is a serine protease that is synthesized as the inactive precursor pre-kallikrein. Kallikrein catalyses the conversion of plasminogen to plasmin. It indirectly leads to increased levels of t-PA by cleaving kininogen to release bradykinin. Bradykinin increases t-PA formation. It also converts factor 12 to 12a, the initiating step in the contact activation pathway (previous intrinsic pathway) of coagulation – an important mechanism during CPB surgery.

2. Pharmacokinetics

Aprotinin is metabolised by lysosomal enzymes, eliminated via proteolysis and partially excreted renally. It has a plasma half-life of 150 min and a terminal half life of 5-10 hours.

3. Dosing regimens

The full-dose regimen is often referred to as the Hammersmith regimen, which consists of a IV loading dose of 280mg after induction of anaesthesia, 280mg added to the cardiopulmonary bypass circuit priming fluid and an infusion of 70mg/hour for the duration of the surgery.
The other common dosing scheme, referred to as the half-dose or the low-dose regimen, involves the loading dose of 140mg after induction of anaesthesia and 140mg added to the cardiopulmonary circuit priming fluid and and infusion of 35mg/hr for the duration of surgery. Most studies that compared the 2 regimens found no clinical or statistically significant difference in blood loss and transfusion requirements between the 2 groups.

A third dosing regimen is reported in the literature, that involves priming the CPB pump with 280mg of aprotinin only. This dose demonstrates similar blood conservation compared to the higher doses with its antifibrinolytic effects but it does not show similar anti-inflammatory effects measured by the cytokine response, complement formation and neutrophil activation.

4. Adverse effects

- Potential thrombogenic effects
- Increased occurances of stroke and myocardial infarction, renal failure, heart failure and death are implied.
- Anaphylactic reactions – to the bovine polypeptide, especially in cases of re-exposure within 6 months
- In a large multicentred trial with EACA, TXA and Aprotonin, the results showed that the risk of bleeding and transfusion was the lowest in the aprotonin group but the mortality was increased in patients receiving aprotonin compared to the other antifibrinolytics. This lead to the early termination of the trial and subsequint withdrawel of aprotonin from the market

5. Uses

The nonspecific protease inhibitor aprotinin has been used successfully to reduce bleeding in cardiac surgery. Unfortunately its safety was questioned and aprotinin was finally withdrawn from marketing in 2007 after a large prospective study demonstrated a trend toward higher mortality. The potential risks of administration include stroke, myocardial infarction, renal insufficiency, immunologic hypersensitivity, premature graft occlusion and death.

Since the drug was reinstated in 2012, the European Medicines Agency noted that aprotinin should only be given to patients as prophylactic use to reduce blood loss and blood transfusions in adult patients who are at high risk of major blood loss undergoing isolated cardiopulmonary bypass graft surgery and only after careful considerations of the benefits and risks.

Safety concerns regarding aprotinin after the publication of the BART (Blood Conservation Using Antifibrinolytics in a Randomized Trial) study lead to the withdrawal of aprotinin in 2007. However, investigators took note of the anti-inflammatory response present in subjects undergoing CPB surgery, which quickly put the spotlight on TXA and lead to the interests in the anti-inflammatory and potential immunomodulatory mechanism of TXA, which is currently being investigated.

Conclusion

Antifibrinolytic agents still play a large role in Patient Blood Management strategies. We as clinicians must make sure that we use it for the correct indications. Tranexamic acid is not a substitute for effective surgical management of any bleeding; it does not contract an atonic uterus, nor does it tie a heavily bleeding vessel or stabilise a fractured pelvis. Tranexamic acid is an effective therapy for fibrinolysis. So even after almost a half a century of use, our current knowledge of this agent beyond coagulation is still limited.

I am looking forward to seeing more research done to really understand the risks associated with this group of drugs as well as the novel uses of antifibrinolytics in clinical practice.

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Notes

Part I Anaesthesia Refresher Course – 2021
University of Cape Town

Functional Neuroanatomy

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Functional neuroanatomy is an enormous topic. I have tried to distil the information that is of relevance to us as anaesthetists.

Functional neurosurgery is an ever-expanding sub-specialty of neurosurgery. Functional Neurosurgeons will treat conditions like chronic pain, spasticity, movement disorders, epilepsy and tumours in eloquent areas of the brain requiring functional cortical mapping. The field of functional neurosurgery is continuing to expand to include treating conditions such as depression, obesity and addictions. Functional neurosurgery doesn't necessarily treat a structural disorder but rather alters the CNS circuitry to affect change within the nervous system.

By 210 AD the brain had become accepted as the seat of voluntary movement, sensation and even intelligence. How exactly it performed these functions remained a mystery, as it still does in many ways today. There is a highly complex relationship between the structure and function of the brain. The localization of brain function was originally studied by observing the effects of certain brain lesions on function. The identification of Broca's and Wernicke's areas in the 1860's/1870's introduced the concept of a relatively static organization of the cerebral cortex into eloquent regions necessary for specific functions, and 'non eloquent' areas that carry out an important but 'non-essential' role in cortical processes that manifest function.

What followed was that based on a patient's symptoms and signs, the location of a lesion in the brain could be identified and a resection could be planned and the postoperative deficits predicted. The first successful resection of a brain tumour was performed in 1881 in a young woman. The surgeon localized the tumour seemingly entirely by his clinical examination of the patient.

Today the modern neurosurgeon aims for maximal tumour resection while preserving function, particularly by preserving the eloquent cortex, but also the subcortical white matter tracts and higher cortical functions.

The Eloquent cortex refers to specific areas of the cortex of the brain that directly control essential functions, where damage to these areas would generally produces major focal neurological deficits. Included in the eloquent cortex are:

- primary motor cortex (precentral gyrus)
- primary somatosensory cortex (postcentral gyrus)
- primary visual cortex
- primary auditory cortex
- Broca's area
- Wernicke's area

Broca and Wernicke provided a starting point for identifying language areas of the brain but in reality the exact localization of language functions has high inter-individual localization variability. The topography of language function is actually so highly variable that it cannot be inferred from anatomical landmarks alone.

The field of neuroscience is moving away from a rigid localizationist view of cerebral function to a more dynamic view that accounts for variability, neuroplasticity and the largescale networks that allow multiple and sometimes distant cortical regions to interact directly or indirectly. For functional oncological neurosurgery, the modern neurosurgeon aims to maximize resection of the tumour while preserving function which means preserving the eloquent cortex **and** subcortical white matter tracts.

Advances in technology have facilitated major advances in the study and understanding of brain function. fMRI has been a breakthrough imaging modality in the study of brain structure and function. Diffusion Tensor Imaging is an MRI modality that can identify major white matter tracts in the brain. However, these imaging modalities lack sensitivity and specificity and are inferior to direct cortical mapping for the identification of eloquent sites. Indeed the gold standard for identification of language areas of the brain is awake cortical mapping.

Awake craniotomy is a procedure where the patient is awake for all or part of the procedure to allow for functional cortical mapping. We must remember as well that the concept of 'eloquence' is relative. While motor, language and visual functions are clearly eloquent areas for all, other higher order functions may be individually important as well, e.g. musicians, careers requiring visual-spatial orientation etc. Eloquence is determined on an individual basis.

Korbinian Brodmann (1868 – 1918) was a German neurologist. He identified 52 cortical areas that differ histologically. This information has been refined over time but his work was an important first step in identifying functional areas of the brain.

Brain function:

Simplistically put there are 4 main brain functions:

1. Mobility
2. Communication
3. Biological Maintenance
4. 'The survival kit'

1. Mobility: The mobility function accounts for a large part of the central and peripheral nervous system. Motor function requires a conscious decision and an unconscious execution of that decision, the latter accounting for 80% of motor circuitry in the brain. In the brain the mobility function is achieved by complex interactions between the prefrontal cortex, precentral gyrus (motor cortex), thalamus, cerebellum, basal ganglia and white matter tracts (corticospinal tracts). From the prefrontal cortex where a decision is made, the message goes to the motor cortex, then to the thalamus then to the lateral cerebellum where a motor programme is organized, the message then goes back to the motor cortex to programme in the group of muscles required for the movement and finally via the corticospinal tract to the correct level of muscle activation. A complimentary circuit connects the cortical area to the basal ganglia which store all of the motor programmes created by training and education. Adjustments to agonist/antagonist signals to muscle groups are performed in the cerebellum and substantia nigra. This multilevel control system requires a close interaction between sensory input and motor output.

2. Communication: This function also occupies a large part of the brain and has 3 main aspects: sensory inputs (visual, auditory), expression outputs and the association pathways (white matter tracts). The recognition and interpretation of spoken and written language occurs unilaterally, in the left hemisphere of most people. Broca's and Wernicke's areas are cortical areas specialized for the production and comprehension, respectively, of human language. Broca's area is found in the left inferior frontal gyrus and Wernicke's area is located in the left posterior superior temporal gyrus. Destructive lesions in the receptive language area (Wernicke's area) results in receptive aphasia which is the inability to understand speech and writing. The production of speech requires an intact expressive speech area (Broca's area) in the frontal lobe. Damage to this area leads to expressive aphasia. Speaking requires the control of 35 different muscles! The language networks in the brain are complex, at least 8 distinct white matter pathways involved in language processing have been identified with injury to any one of those tracts resulting in some form of language deficit. In fact recovery from cortical injury after surgery is more possible that recovery from an injury to the white matter tracts which display less plasticity and redundancy.

3. Biological maintenance: All biological maintenance services/homeostatic mechanisms are automated e.g. breathing, cardiac rhythm, BP regulation, gastric mobility, metabolism, endocrine regulation. This autonomic nervous system has its headquarters in the hypothalamus.

4. 'The survival kit': This is integrated in the limbic system and includes the 'emotions' circuitry: hippocampus/mammillary bodies/anterior thalamus, cingulate gyrus etc. The formation of new memories occurs in the circuitry of the hippocampus which is inside the temporal lobe. Bilateral interruption in hippocampal circuitry results in loss of the ability to form new memories. Older memories can still be recalled as they are stored diffusely throughout the cerebral cortex.

Functional brain anatomy

Embryonic development

The brain develops from a simple tube into a very complex structure. All of the CNS derives from ectoderm. At 4 weeks gestation, the neural tube will have developed three outpouchings that will give rise to the different components of the brain. These outpouchings are the Forebrain (cerebrum and diencephalon), Midbrain and Hindbrain (pons, medulla and cerebellum)

Functionally it is preferable to divide the brain into 4 main areas:

1. Cerebral hemispheres
2. Diencephalon
3. Brainstem and cranial nerves
4. Cerebellum

1. Cerebral hemispheres

Anatomy of the cerebral hemispheres:

The cerebral hemispheres make up the largest portion of the brain (85% of total brain mass). They cover the diencephalon and the upper brainstem. The cortex is folded into a unique pattern of gyri (hills) and sulci (valleys). This characteristic pattern of gyri and sulci allows us to divide the brain into different functional areas. A fissure is a deep sulcus. The cortex has primary functional sites (e.g. primary motor cortex, visual cortex) and then association areas (prefrontal cortex, sensory association cortex). Association areas are where higher order functioning happens. These parts of the brain take in multiple inputs and associate them with one another to comprehend our world. White matter tracts/pathways connect all of these areas and so are crucial to function.

The neuron is the brains most basic working unit. The grey matter of the brain is made up of neuronal cell bodies and dendrites as well as other support cells while the white matter is made up of myelinated axons. There are 2 cerebral hemispheres connected by the corpus callosum. Each hemisphere is divided into 4 lobes:

The frontal lobe is the most complex part of the human brain. This, the largest brain lobe, is responsible for executive function. This is where reasoning, decision-making, sensory integration, planning, and execution of movement occur. The frontal lobe is made up of the prefrontal cortex, premotor cortex, primary motor cortex.

The parietal lobe is the home of the somatosensory cortex and association areas, the area of the brain responsible for processing sensation and touch information, as well as some aspects of spatial processing.

The temporal lobe is the major processing center of sound (including language) and some forms of memory. Epilepsy affects about 1% of the population. About two thirds of patients will achieve seizure control on medication but for the remaining third with resistant seizures, epilepsy surgery might be

considered. Surgery is most successful in patients with temporal lobe epilepsy (TLE). Most patients with TLE have seizures that originate from the mesial-basal temporal lobe structures (hippocampus and amygdala).

The occipital lobe is mainly responsible for processing and interpreting visual information. It is made up of the primary visual cortex and visual association areas.

These lobes are separated by sulci/fissures. When looking at the lateral brain surface, the central sulcus separates the frontal and parietal lobe, Sylvian (lateral) fissure separates frontal and temporal lobe, the pre-occipital notch defines the occipital lobe. The transverse fissure divides the supra-tentorial space from infra-tentorial space. When looking at the// superior surface of brain one can see the interhemispheric fissure.

Functional areas of the cerebral hemispheres:

The function of the cerebral cortex is essentially integration and interpretation of information.

A. Prefrontal cortex (technically an association area). Most complex, most developed in humans. Closest to where our 'mind 'sits. Complex behaviours, social behavior, decision-making, cognitive function, expression, personality, executive functions, impulse control, working memory (short term memory).

B. Motor areas:

Primary motor cortex (precentral gyrus): This is a distinct anatomic region occupying the posterior part of the frontal lobe. This area contains a representation of all muscles of the body according to a topographical code called the 'homunculus'. This somatotopic organization shows the large lateral parts of the motor cortex representing face and hand contrasting with the relatively small area devoted to the lower limbs medially. Important for motor movement.

Premotor cortex: In front of primary motor cortex, close to prefrontal cortex. This area receives highly processed sensory information and is responsible for motor planning.

Frontal eye field: Anterior to premotor cortex and controls voluntary eye movement.

Broca's area: An association area, manages speech production (speech, hand signs, written word) located next to motor homunculus where hands and mouth are represented.

C. Sensory areas: A large portion of the brain is dedicated to sensory processing and allows us to understand the world around us and interpret stimuli as they arrive in the cortex.

Primary somatosensory cortex (Postcentral gyrus): Somatotopic organization in the form of a sensory homunculus. Again distribution is biased towards face, mouth and hand with high sensory discrimination in these areas.

Somatosensory association cortex: Posterior to primary sensory cortex. Integrates different sensory inputs from vision, smell, auditory, touch etc. There is a primary sensory cortex for each sensation we have and inputs from all of these areas come together in the parieto-temporal somatosensory association cortex where the information is processed and comprehended.

Auditory areas: Primary auditory cortex in the superior temporal lobe and auditory association areas posterior to primary auditory cortex. Wernicke's area is an auditory association area that evaluates sound.

Others sensory areas: Gustatory cortex, vestibular cortex, olfactory cortex.

D. Vision:

Primary visual cortex: Sits posteriorly, mostly on the medial aspect of brain. Visual input from the eyes, travels through the thalamus, into the occipital lobe. The visual cortex will detect a flash of light but understanding/identifying the signal happens in the association areas.

Visual association areas: Interpret colour, form and movement. This is where comprehension of the information received by the primary visual cortex occurs.
Information from the primary occipital cortex goes forward into the association areas in 2 different streams:
Dorsal stream (parietal): Where an object is.
Ventral stream (temporal): What an object is (face recognition, naming etc.)

E. Deep Grey Matter:

There are many areas of deep grey matter in the cerebral hemispheres. One example of deep grey matter is the Basal Ganglia made up of a number of nuclei: Corpus Striatum, Substantia Nigra in the midbrain, Subthalamic Nucleus. Motor processing occurs here with the regulation of the intensity of voluntary movement. This area regulates and controls motor impulses from the cortex. Parkinson's disease is a result of the degeneration of dopamine producing neurons of the Substantia Nigra.

2. Diencephalon (thalamus and hypothalamus)

The diencephalon is composed of four major portions: the epithalamus, subthalamus, hypothalamus, and thalamus.

Thalamus: 'inner room'. Sits deep in the middle of the brain**.** The thalamus is the most substantial portion of the diencephalon, situated deep in the middle of the brain as two large oval masses flanking the third ventricle. The thalamus serves as a relay point for all sensory input tracts. It sorts sensory input and decides where it must go. The anatomy of the thalamus is extremely complex. There is a lot of research into how the thalamus functions and how we can potentially modulate thalamic function.

Hypothalamus: Situated below the thalamus. The hypothalamus functions on its own, it is not a relay centre. It is responsible for basic autonomic functions; homeostasis, emotional responses, body temperature, hunger, thirst, satiety function, sleep-wake cycle, pituitary gland function, memory.

3. Brainstem

Located in the posterior cranial fossa the brainstem is the structure that connects the cerebrum of the brain to the spinal cord and cerebellum. It is composed of 3 main parts in descending order: the midbrain, the pons, and the medulla oblongata. The midbrain is continuous with the diencephalon and in some texts it is included as part of the brainstem. The brainstem is responsible for automatic, programmed, reflexive behaviours, functions that are vital to life, such as breathing, consciousness, blood pressure, heart rate, and sleep. The brainstem contains many critical collections of white and grey matter and is a passageway between the spinal cord and the cerebrum. Ten of the twelve cranial nerves arise from their cranial nerve nuclei in the brainstem.

Midbrain: CN 111, 1V. The midbrain serves as the connection between the pons and the diencephalon. It also connects posteriorly to the cerebellum via the superior cerebellar peduncles. The midbrain includes many important nuclei including but not limited to the substantia nigra at the base of the midbrain, the red nucleus anterior medially at the level of the superior colliculus, and the dorsal raphe nucleus. The substantia nigra contains dopaminergic neurons that help to regulate movement associated with the basal ganglia. The red nucleus is involved with movement and contains many connections with the cerebellum.

Pons: CN V, V1, V11, V111. The pons connects the medulla oblongata inferiorly to the midbrain superiorly. Important nuclei of the pons include the cranial nerve nuclei, the locus coeruleus, and pontine nuclei. The neurons of the locus coeruleus produce norepinephrine and have projections that spread widely throughout the CNS. The locus coeruleus is involved in the reticular activating system and suffers compromise in Alzheimers disease .The pontine nuclei are a collection of pontine motor

nuclei in the anterior pons that have many connections with the cerebellum and assist with coordinating movement and help to modulate breathing.

Medulla: CN 1X – X11. The most inferior portion of the midbrain is the medulla oblongata, which connects the pons to the spinal cord. It meets the spinal cord at the level of the foramen magnum. The reticular formation is located in the medulla oblongata.

Major Brainstem Tracts

The Reticular Formation is a major brainstem tract. The reticular formation is found in the anterior portion of the brainstem and is composed of multiple tracts that have a large number of connections. The reticular formation extends from the spinal cord through the brainstem to the diencephalon. It receives input from various tracts including, spinothalamic tracts, spinoreticular tracts, the dorsal column-medial lemniscus pathway, visual pathways, auditory pathways, vestibular pathways, and cerebelloreticular pathways. The reticular formation sends efferent fibers to the thalamic nuclei, cerebellum, red nucleus, corpus striatum, substantia nigra, hypothalamus, and subthalamic nucleus. The vast connections of the reticular formation allow it to modulate many different functions; some of these include movement coordination, autonomic regulation of blood pressure, heart rate, and respiratory rate, postural reflexes, neuro-vegetative reflexes, and taste. It also plays a role in wakefulness and sleep.

Persistent vegetative state- loss of only cortical functions with intact brain stem functions.

Brain-stem death- absent brain stem reflexes but the presence of few cortical areas of activity as well as hypothalamic integrity such as osmoregulation.

Whole Brain death- biological death with absent cortical and brainstem functions.

4. Cerebellum

The cerebellum or ‘little brain’ sits in the posterior fossa, dorsal to the brainstem (11% of brain mass). Its main function is to co-ordinate movement and maintain posture and equilibrium. It has folia and fissures. The central part of the cerebellum controls axial movement of the head, neck and trunk while the lateral cerebellum controls appendicular movement. Sensory Input to the cerebellum comes from the cerebral cortex, proprioceptive information and equilibrium information.

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2. Atlas of Morphology and Functional Anatomy of the brain. T. Scarabino, U. Salvolini
3. Neurosurgical operative atlas. Functional Neurosurgery. 3rd Edition. R Gross, N Boulis
4. Anaesthesia for awake craniotomy. C. Burnand. BJA CCEAPD. Vol 14, issue 1, Feb 2014.

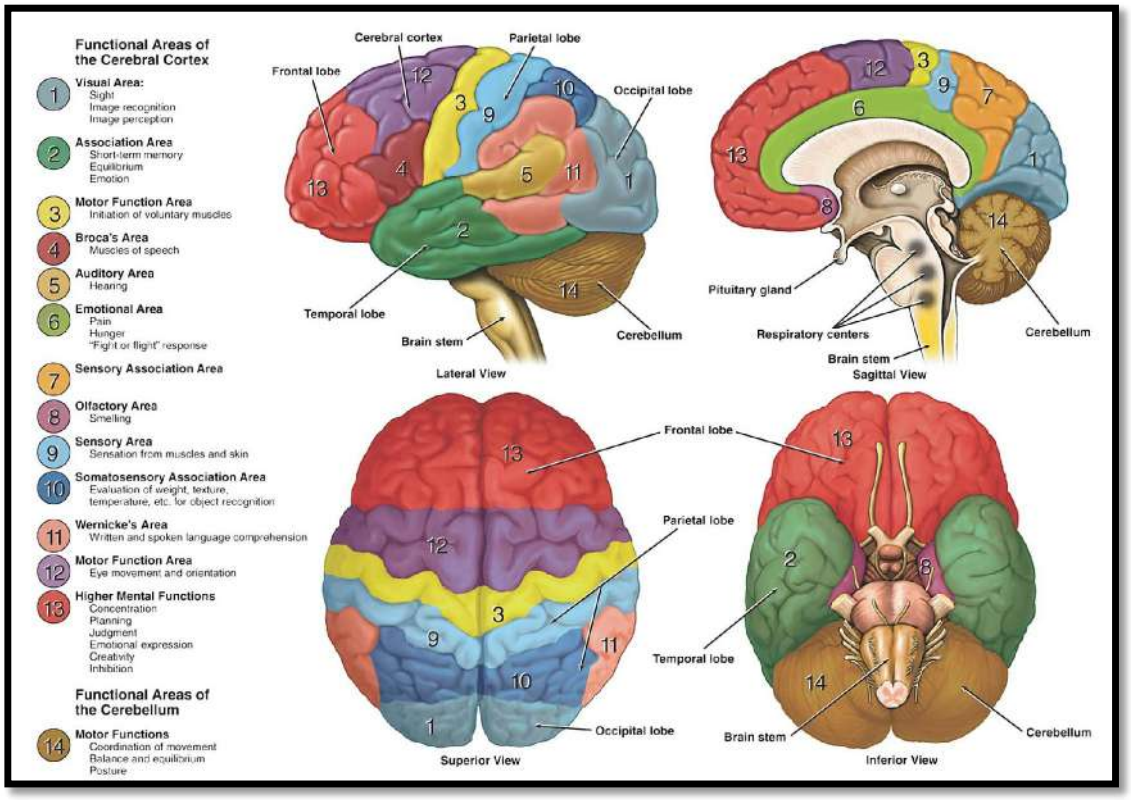

Image 1: Functional areas of the cerebral cortex

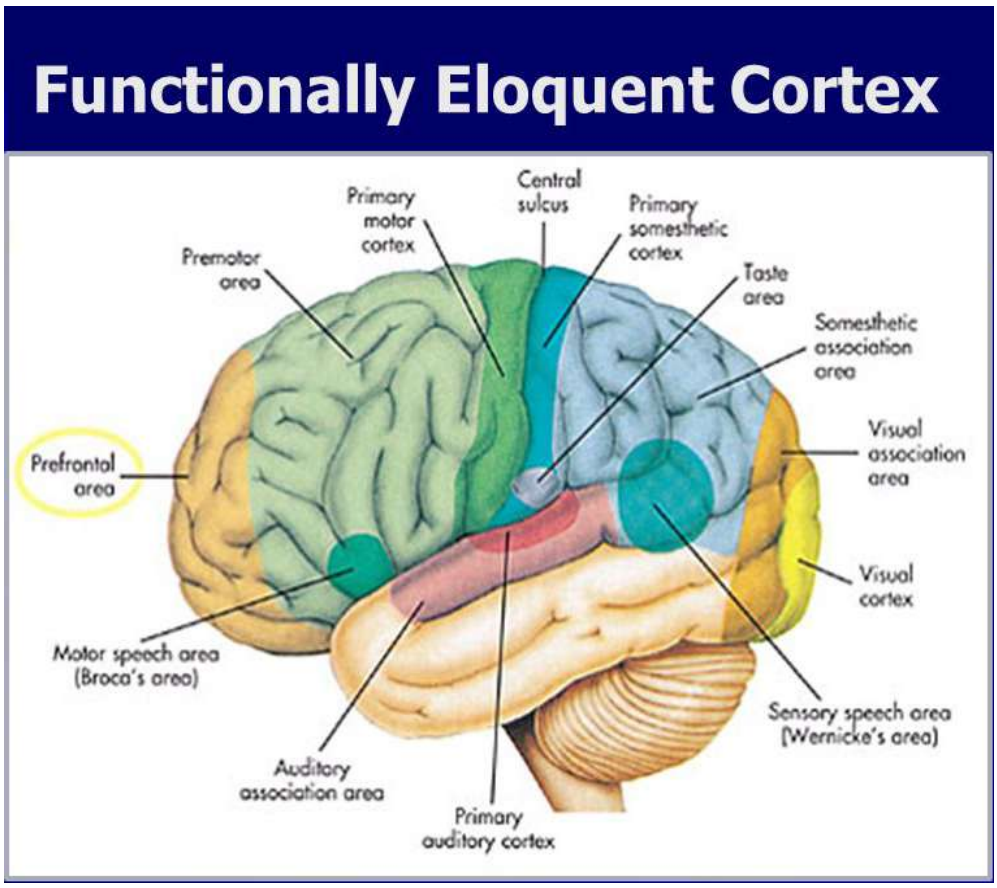

Image 2: The eloquent cortex

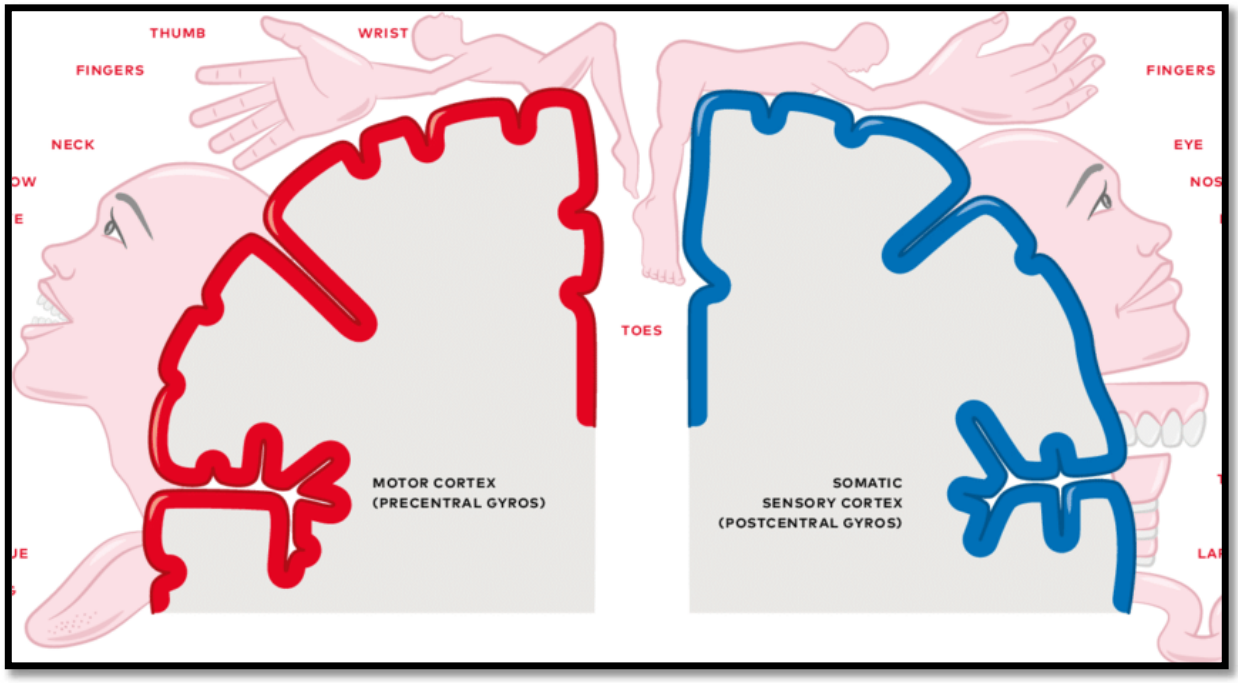

Image 3: The motor and sensory homunculus

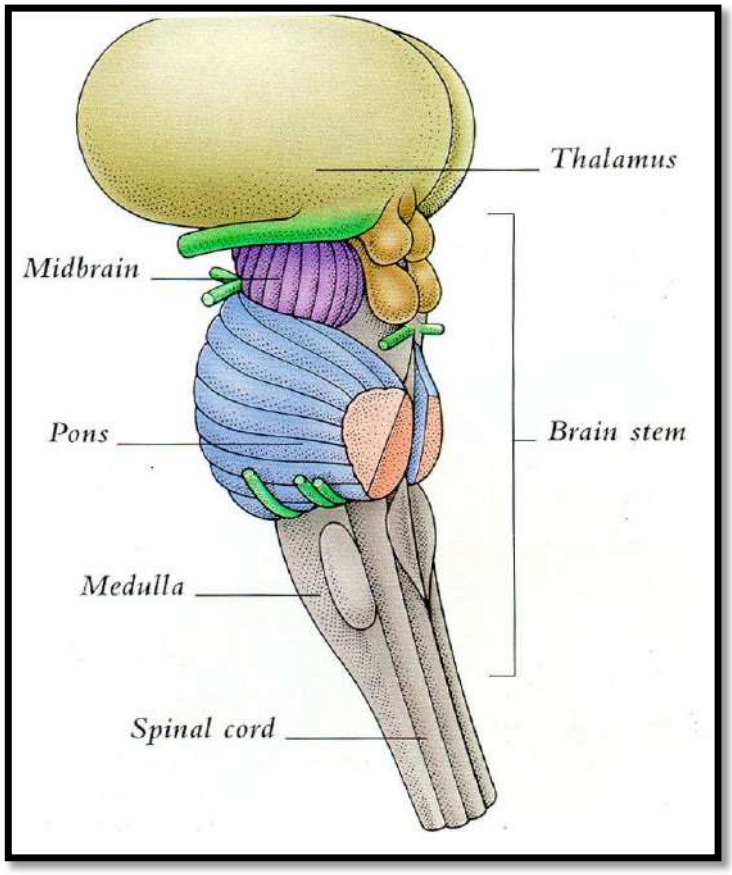

Image 4: The Brainstem

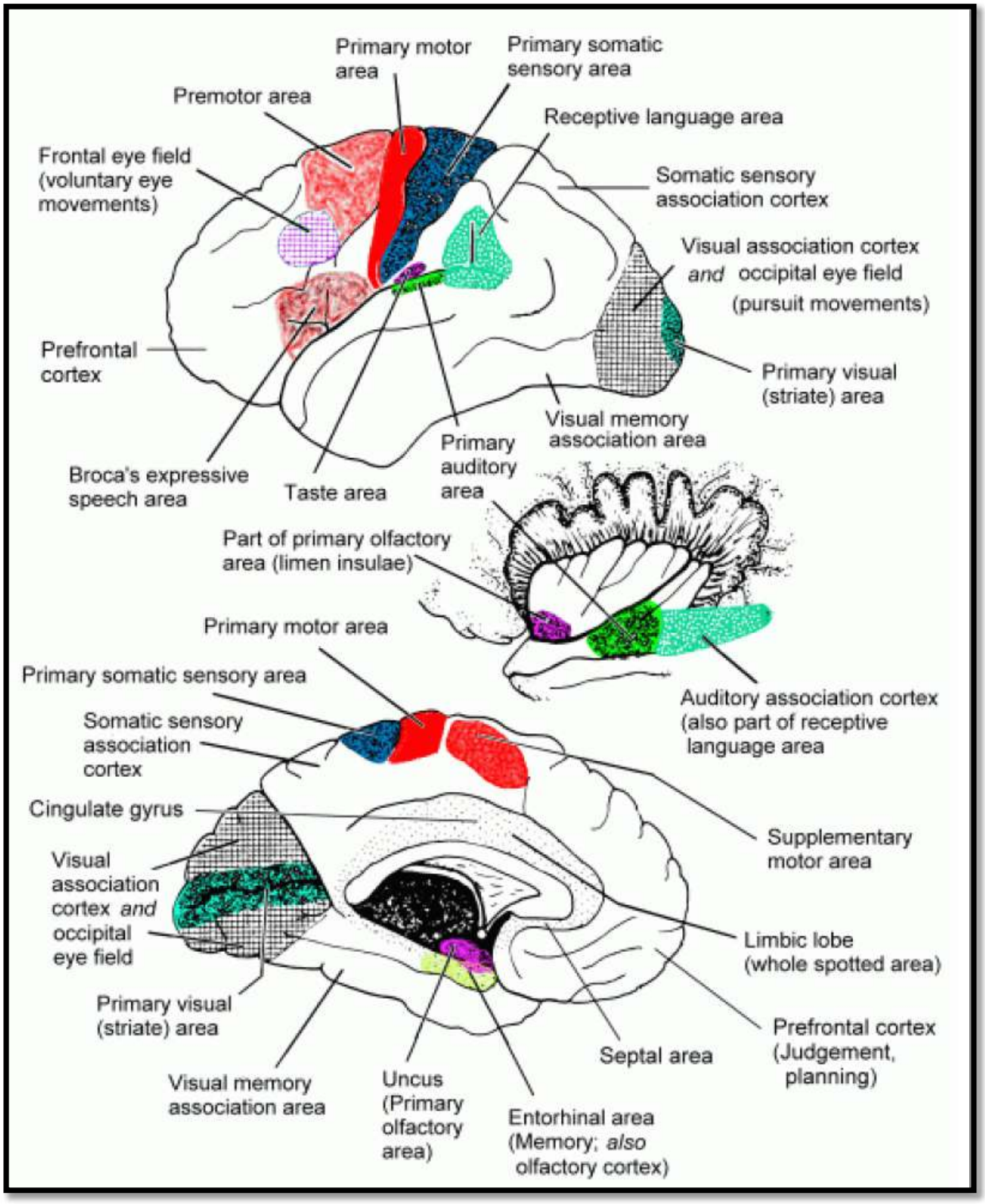

Image 5: Functional cortical localisation

Notes

Vascular tone

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Introduction

Blood vessels are responsible for delivering blood through the cardiovascular system.
Depending on the needs of the body they can proliferate, adjust their tone, and even pulsate.
Vascular tone regulation plays an important role in maintaining tissue and circulatory haemostasis.
Blood flow autoregulation is an essential ability of individual organs to change vascular tone in order to maintain constant blood flow at a variety of different pressures.

The vasculature and vascular smooth muscle

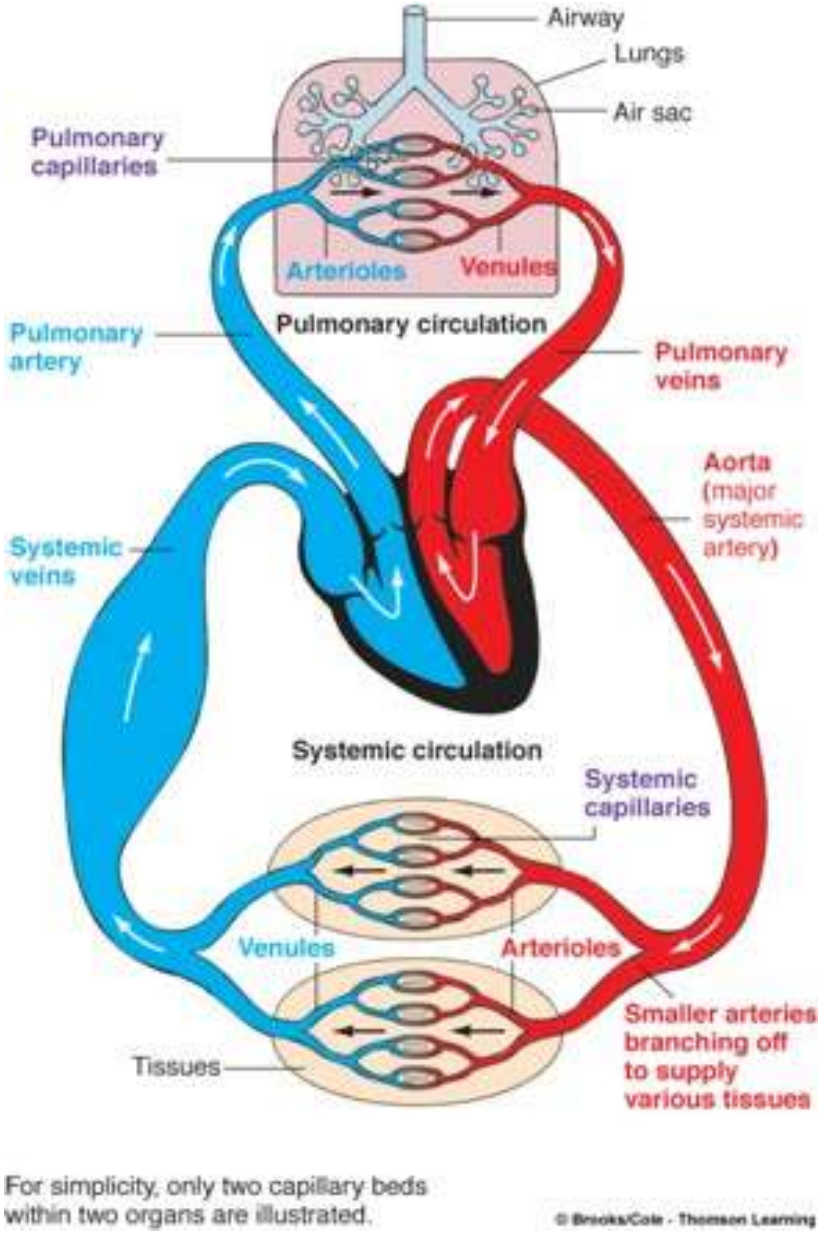

Image from Austin community college lecture on cardiovascular system
Image available from https://www.austincc.edu/apreview/PhysText/Vascular.html

Graphic illustration of different vessels

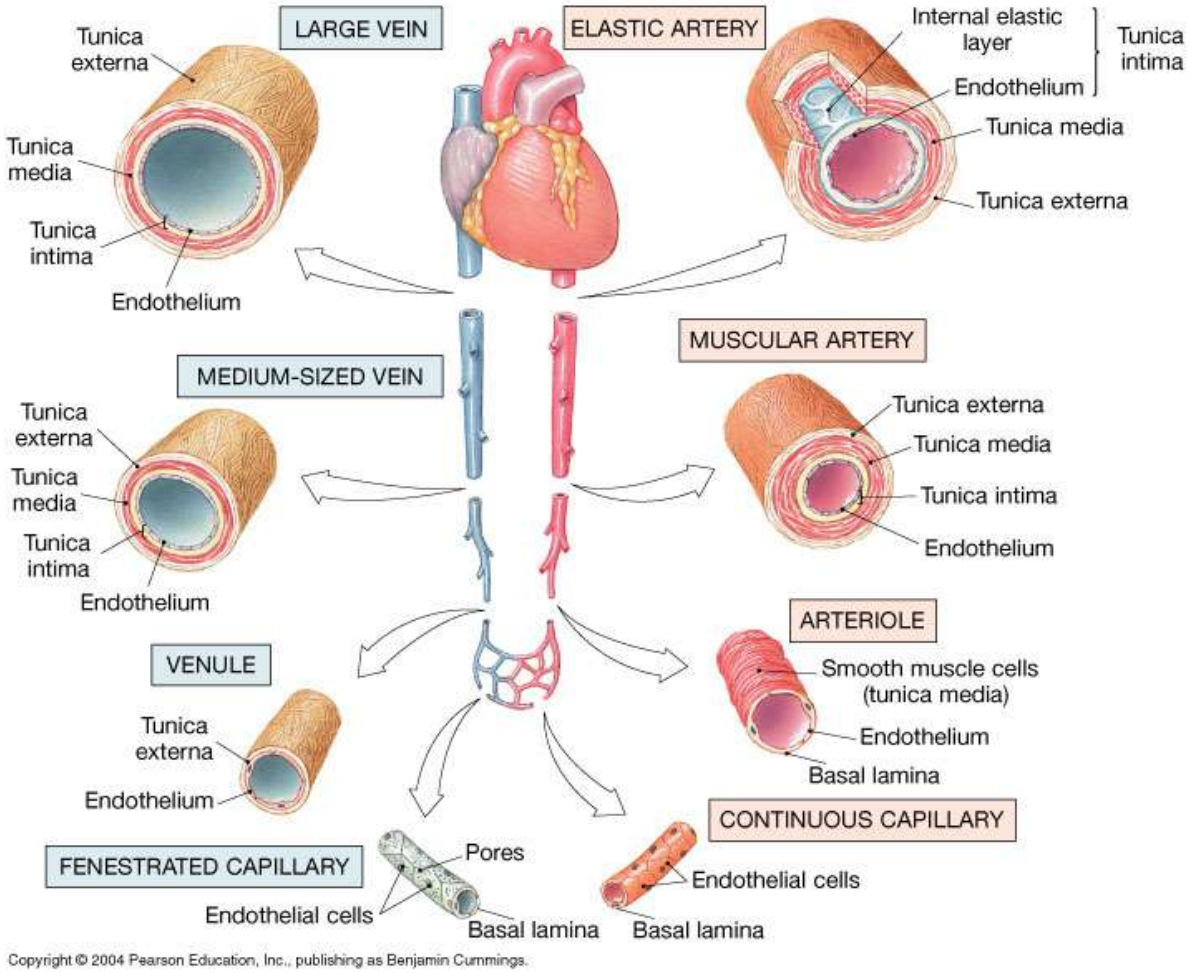

Image graphically describing types of vessels.
Image available from:
http://websupport1.citytech.cuny.edu/Faculty/ibarjis/Teaching/Anatomy%20and%20Physiology/lecture21/Lecture/Lecture1.htm

Vasculature can simplistically be classified into three main types: arteries, capillaries, and veins. Arteries and veins contain three main layers: a tunica intima, tunica media, and tunica externa. Comparing arteries

- Arteries have a thicker tunica media.
- Veins have a thicker tunica externa.

Capillaries only have a tunica intima that can be as thin as one cell layer thick.

The vascular tree is a closed system of vessels consisting of:

Arteries

Carry blood from heart to tissues.
Contains roughly 10% of total blood volume.
Consist of three layers:

- Innermost layer, the tunica intima (also called tunica interna),
  - simple squamous epithelium surrounded by a connective tissue basement membrane with elastic fibres
- Middle layer, the tunica media,
  - primarily smooth muscle and is usually the thickest layer.
  - Influence's vessel diameter
- Outermost layer, the tunica externa or tunica adventitia.
  - Attaches the vessel to the surrounding tissue.
  - Connective tissue with varying amounts of elastic and collagenous fibres.

- The connective tissue is quite dense where it is adjacent to the tunic media but becomes lose connective tissue near the periphery of the vessel.

Main Subtypes

- Elastic arteries (Aorta)
  - Largest diameter
  - Exposed to high pressure fluctuations.
  - Pressure reservoir
  - Elastic recoil propels blood forward during diastole.
- Medium arteries
  - Regulate blood supply (Vasoconstriction/Vasodilation)
- Arterioles
  - Are smaller branches of arteries.
  - Regulate blood flow into capillaries.

Capillaries

Smallest and most numerous of vessels.
Where all exchanges are made with surrounding cells.
Contains roughly 5% of total blood volume.
Distribution varies according to metabolic needs of individual tissues.
Highly active tissues such as the kidneys have extensive capillary networks.
Lens and cornea of the eye completely lack a capillary network.

Venules and Veins

Blood from capillaries drain into venules – progressively drains into larger veins until reaches the heart.
Contains almost 70% of total blood volume.
Have the same three layers as the arteries.

- Contains less smooth muscle and connective tissue.
- Walls thinner and less rigid
- Medium and large veins contain valves.

Table of differences

	Arteries	Capillaries	Veins
Function	Carry blood **away** from the heart at **high** pressure	-Supply all cells with their **requirements** -Take away **waste** products	**Return** blood to the heart at **low** pressure
Structure of wall	-**Thick**, strong -Contain **muscles**, **elastic** fibres and **fibrous** tissue	**Very thin**, only one cell thick	-**Thin** -Mainly **fibrous** tissue -Contain far **less muscle** and **elastic** tissue than arteries
Lumen	-**Narrow** -Varies with heartbeat (increases as a pulse of blood passes through)	-**Very narrow** -Just wide enough for a red blood cell to pass through	**Wide**
Valves	(-)	(-)	(+) Prevent backflow
How structure fits function	-Strength and elasticity needed to withstand the pulsing of the blood, prevent bursting and maintain pressure wave -Helps to maintain **high blood pressure**, preventing blood flowing backwards	- No need for strong walls, as most of the blood pressure has been lost -Thin walls and narrow lumen bring blood into close contact with body tissue, allowing **diffusion** of materials between capillary and surrounding tissues. -White blood cells can squeeze between cells of the wall	- No need for strong walls, as most of the blood pressure has been lost - Wide lumen offers **less resistance** to blood flow

Images from The Human Circulation http://humancirculatorysystemfall2014.weebly.com/blood-vessels.html
Chart from http://biology-igcse.weebly.com/uploads/1/5/0/7/15070316/1723180_orig.png

Vascular tone

Vascular tone refers to the degree of constriction experienced by a blood vessel relative to its maximally dilated state.
Majority of vessels exhibit some degree of smooth muscle contraction under basal conditions.
The balance in vascular tone is determined by many different competing vasoconstrictor and vasodilator influences acting on the blood vessel.

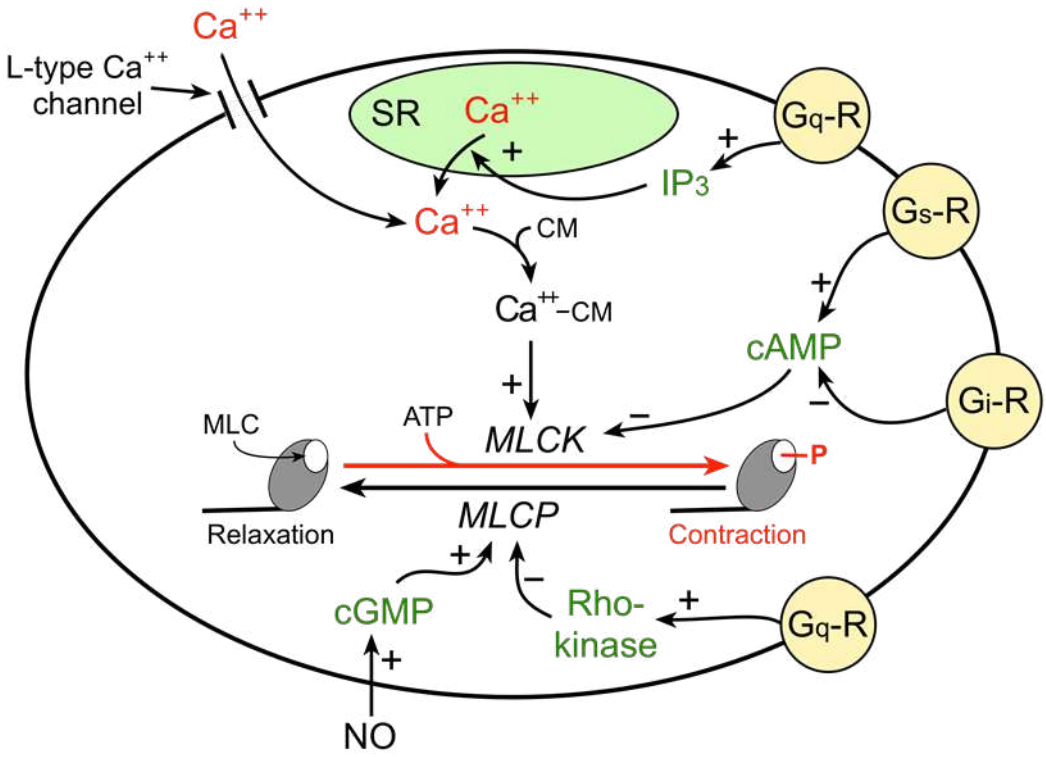

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Image available https://cvphysiology.com/Blood%20Pressure/BP026

Mechanisms leading constriction or relaxation of blood vessels is mainly due to influences on the interaction between actin and myosin.

Some differences between Vascular smooth muscle (VSM) and cardiac muscle.

- Vascular smooth muscle undergoes slow, sustained tonic contractions.
- The regulatory protein, Troponin, is usually absent.
- Actin and myosin in VSM are not organized into distinct bands. Their arrangement makes them well suited in maintaining tonic contractions and reducing lumen diameter.

Balance of intracellular calcium concentrations is particularly important in regulating smooth muscle contraction.
The mechanism by which an increase in intracellular calcium stimulates VSM contraction is illustrated in the figure above.

- Increase in free intracellular calcium.
  - Increased flux of calcium into the cell through calcium channels or
  - Release of calcium from internal stores (e.g., sarcoplasmic reticulum(SR)).
- Free calcium binds to a special calcium binding protein (calmodulin).
- Calcium-calmodulin activates myosin light chain kinase (MLCK), an enzyme responsible for phosphorylating the myosin light chains (MLC) on the myosin heads. (Requires ATP).
- MLC phosphorylation leads to cross-bridge formation between the myosin heads and the actin filaments.
- This results in VSM contraction.

VSM relaxation occurs when there is reduced phosphorylation of MLC.

Mechanisms are:

- Decrease in free Ca.
  - Reduced release of calcium by the SR or reduced calcium entry into the cell
  - Calcium moves either back into the Sarcoplasmic reticulum via a ATP-dependent calcium pump or,
  - Calcium is removed from the cell to the external environment by either a ATP-dependent calcium pump or by the sodium-calcium exchanger
- Inhibition of MLCK by increased intracellular concentration of cAMP,
- Phosphatase-activated MLC dephosphorylation.

G-protein Linked Vascular Receptors and their Biological Agonists

G-protein	2nd Messenger	Receptor	Biological Agonist
Gs	↑cAMP	β_2	Epinephrine
		A_2	Adenosine
		IP	Prostacyclin
Gi	↓cAMP	α_2	Norepinephrine/ Epinephrine
Gq	↑IP_3 & ↑Rho-kinase	α_1	Norepinephrine/ Epinephrine
		ET_A	Endothelin-1
		AT_1	Angiotensin II
		V_1	Vasopressin

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G-protein-couple signal transduction regulates the degree of MLC phosphorylation. (Thus, VSM tone)

Vascular receptors and their agonist.
Gq-protein (SR release of calcium (IP_3 mediated) and activates Rho-kinase, which inhibits MLC phosphatase)

- Noradrenaline (alpha$_1$-adrenoceptors)
- Angiotensin II (AT_1 receptors), endothelin-1 (ET_A receptors) and vasopressin (V_1 receptors)

Gs-protein (inhibits MLCK thereby reducing MLC phosphorylation and relaxing the VSM)

- Adrenaline (beta$_2$-adrenoceptors),
- Adenosine (A_2 purinergic receptors) and prostacyclin (IP receptors

Gi-protein (elicits contraction by reducing cAMP, which increases the activity of MLCK)

- Noradrenaline binding to alpha$_2$-adrenoceptors.

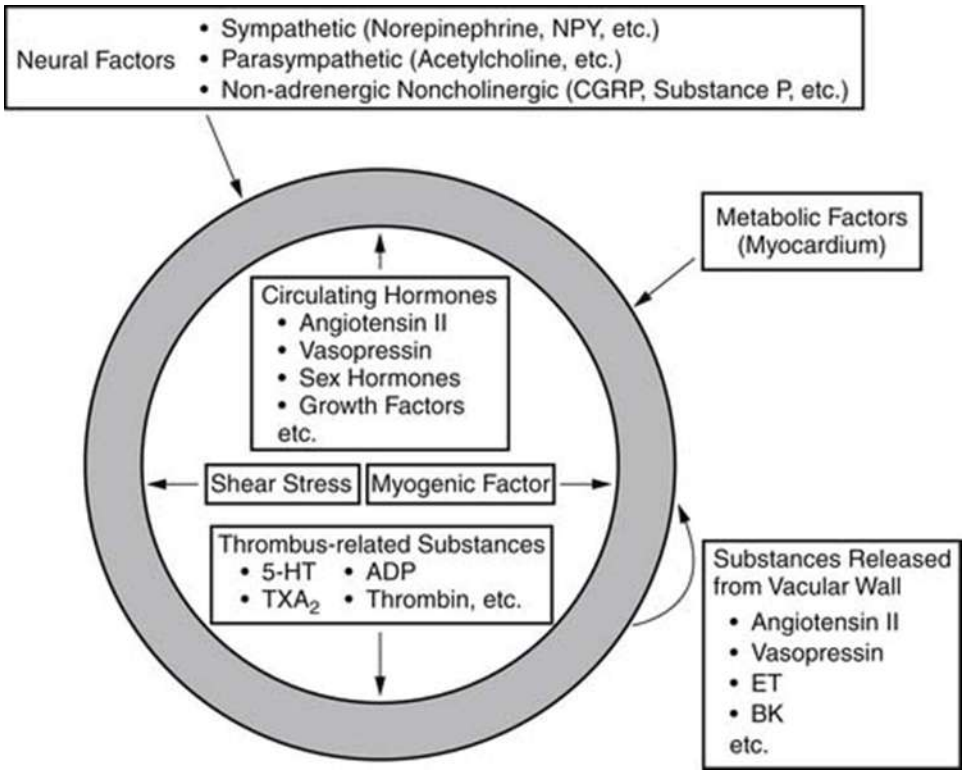
Factors acting on VSM tone

One of the most fundamental principles of circulatory function is the ability of each tissue to control its own local blood flow in proportion to its metabolic needs.

Main needs leading to adjustment of vascular tone.

- Delivery of oxygen
- Delivery of other nutrients
- Removal of CO2

- Removal of other metabolic by-products
- Maintenance of ion concentration
- Transport of various hormones and related substances to tissues
- Other individual tissue functions
    - Blood flow to skin help control temperature loss.
    - Adequate blood flow to kidneys allows excretion of by-products.



Mechanisms of tone control

Acute Control (Seconds to minutes)

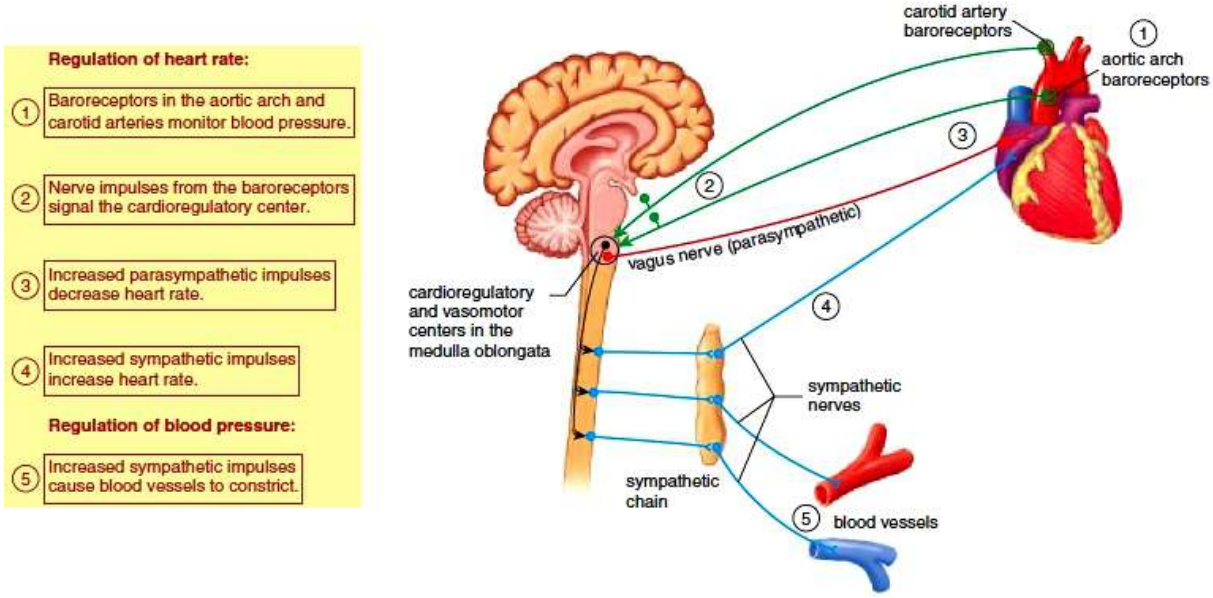


*Figure 12.9 from **www.encyclopedia.lubopitko-bg.com** the Cardiac cycle and Heart sounds*
Figure name: The cardio regulatory centre regulates the heart rate, and the vasomotor centre regulates constriction of blood vessels, according to input received from baroreceptors in the carotid artery and aortic arch.
Image available at http://encyclopedia.lubopitko-bg.com/Cardiac_Cycle_and_Heart_Sounds.html

Extrinsic factors: (Originate outside the organ/tissue)
Primary function of extrinsic factors is to regulate arterial blood pressure by altering systemic vascular resistance

- Neural influences such as sympathetic nerve activation
    - Baroreceptor Reflexes
        - Baroreceptors are sensory receptors that detect changes in blood pressure.
        - Baroreceptors are located in the carotid sinus, aortic arch, and other arteries.
        - Changes in peripheral resistance, heart rate, and stroke volume occur in response to changes in blood pressure.
    - Chemoreceptor Reflexes
        - Chemoreceptors are sensory receptors sensitive to oxygen, carbon dioxide, and pH levels of blood.
    - Central Nervous System Ischemic Response (CNS)
        - Results from high carbon dioxide or low pH levels in medulla and increases peripheral resistance.
- Parasympathetic nervous system innervation is limited.
    - Promotes vasodilation to the digestive tract, external genitalia, and salivary glands.
    - Less important than sympathetic nervous system in control of vascular smooth muscle tone.
    - Parasympathetic endings in arterioles promote vasodilation.
- Hormonal influences
    - That increased vascular tone:
        - Angiotensin II (Very powerful vasoconstrictor. (one millionth of a gram can increase systolic BP by more than 50 mmHg)
        - Noradrenaline (NA) is especially potent vasoconstrictor.
            - During physiological stressful situations NA usually gets released at the sympathetic nerve endings.
        - Vasopressin
            - More powerful than angiotensin
    - That decrease vascular tone:
        - Atrial natriuretic peptide.

Intrinsic factors: (Originate inside tissue/vessel)

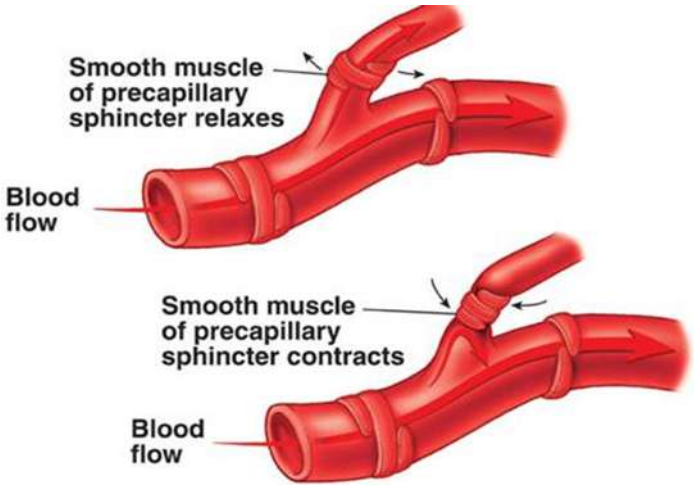


Image from Austin community college lecture on cardiovascular system
Image available from https://www.austincc.edu/apreview/PhysText/Vascular.html

Important for local blood flow regulation within an organ
When evaluating precapillary sphincters under the microscope, they are found to be either completely closed or open.
The number of precapillary sphincters open or closed is proportional to the tissue requirements.
These have also been noted to open and close cyclically several times per minute.
Other substance deficiencies have also been noted to have effects on tissue blood flow for instance glucose, amino acids, vitamins especially Vit B.

Rapid changes in local vasodilation or vasoconstriction of the arterioles and precapillary sphincters.

- Myogenic mechanisms (originating from vascular smooth muscle), which increase tone.
- Endothelial factors such as nitric oxide and endothelin can either decrease or increase tone, respectively.
- Local hormones/chemical substances (e.g., arachidonic acid metabolites, bradykinin, acetylcholine) can either increase or decrease tone.
- Metabolic by-products or hypoxia, which generally decrease tone.
    - As metabolism increases, blood flow increases.
        - an increase in metabolism of roughly 8 times increases blood flow fourfold.
    - As oxygen delivery decreases blood flow increases.
        - when oxygen levels at the tissue drop to roughly 25% the blood flow will increase threefold.

Two theories exist regarding metabolic or hypoxia mechanisms of vasodilation.

Vasodilator theory

Decrease availability of nutrients lead to increased production of vasodilator substances.
These substances then diffuse through the tissue back to precapillary sphincters, meta-arterioles and arterioles leading to vasodilation.

- Substances include:
    - Adenosine, CO2, adenosine phosphate compounds, histamine, potassium ions, and hydrogen ions.

Concern with this theory is the difficulty to show that sufficient amount of vasodilatory substances are produced. It is likely that a combination of vasodilatory substances causes this effect.

Oxygen lack theory

This theory stems from oxygen are required to maintain vascular muscle contraction.

In general, the level of tissue metabolism determines level of blood flow.
For instance, glandular tissue receives large blood flows (Adrenals and thyroid)
Highly metabolic active organs receive high blood flow for instance the liver receives 95ml/100g/min.
Interestingly ***inactive*** muscles, despite constituting 30 -40% of the body mass roughly only 4ml/100g/min but with increasing activity can increase up 20-fold (80ml/100g/min).
It is important that systemic macrovascular changes can accommodate the local tissue demands.
This is can usually achieved by

- Endothelial cells lining the microvascular arterioles release endothelial-derived relaxing factors (EDRF) which is mostly made up of nitric oxide (NO half-life of 6 seconds)
- Rapid blood flow through the small vessels causes viscous drag and increased shear stress on the endothelial cells which leads to great increases in NO.
- Increase in other metabolic by products.
- Extrinsic factors also play a role
    - Neurohormonal changes

	Percent of Cardiac Output	ml/min	ml/min/100g of Tissue Weight
Brain	14	700	50
Heart	4	200	70
Bronchi	2	100	25
Kidneys	22	1100	360
Liver	27	1350	95
Portal	(21)	1050	
Arterial	(6)	300	
Muscle (inactive state)	15	750	4
Bone	5	250	3
Skin (cool weather)	6	300	3
Thyroid gland	1	50	160
Adrenal glands	0.5	25	300
Other tissues	3.5	175	1.3
Total	100.0	5000	

Chronic control (Days to months)

Usually better and more effective control in proportion to tissue needs.
Increase or decrease in both size and number of vessels.

- Related to long term metabolic and oxygen needs.
- Vascular growth determined by maximum and not the average tissue requirement.
- Reconstruction of tissue vasculature can occur rapidly (days) especially in the very young animals and in new growth tissue (cancerous or scar tissue).

Examples are increased oxygen leading to blood vessel overgrowth in the eyes or lungs of neonates (retrolental fibroplasia or bronchopulmonary dysplasia)

Vessel growth
Multiple factors influence vessel growth.
Majority are small peptides and called angiogenic factors.

- Three most important are:
  - vascular endothelial growth factor (VEGF), fibroblast growth factor, and angiogenin.

Certain substances have the opposite effect causing dissolution of vascular cells, for instance some steroid hormones.

Collateral flow formation

- When artery is blocked a new channel is formed around the blockage, leading to at least partial return of blood supply.
- First stage is the dilation of already existing collateral blood vessels, happens within minutes. (Usually initially only 25% effective)
- Further opening does occur over the next few hours to days.
- Further channels develop – usually enough to meet tissue requirements at rest.

Circulatory effect of changes in vascular tone

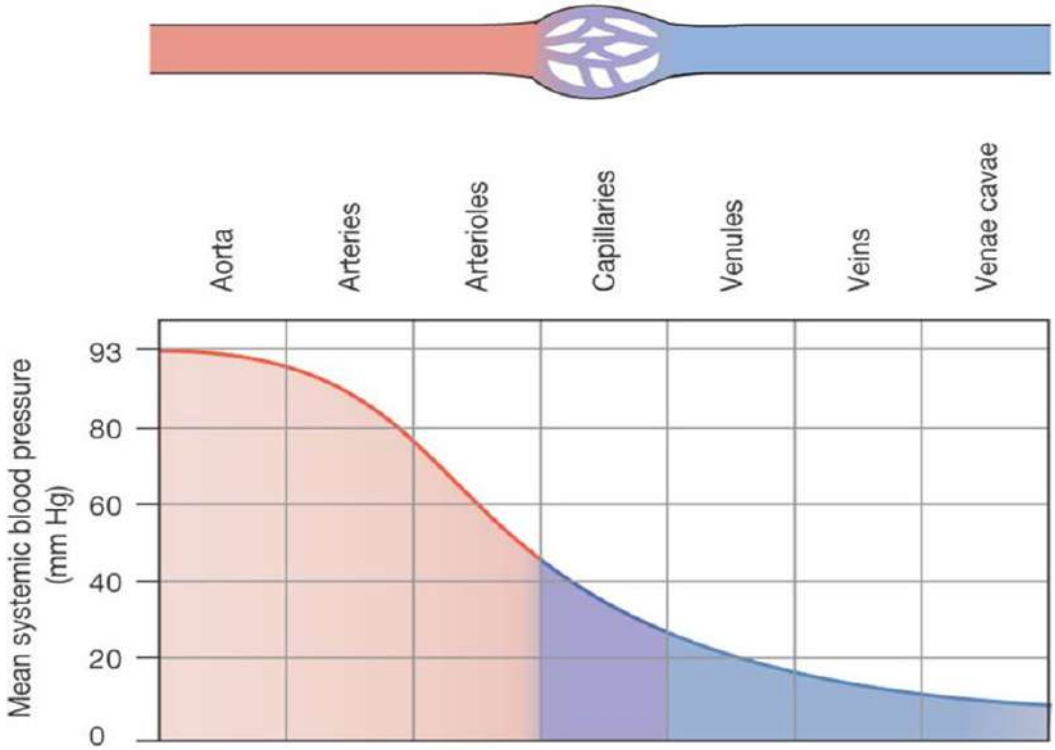


Image from Austin community college lecture on cardiovascular system
Image available from https://www.austincc.edu/apreview/PhysText/Vascular.html

Blood flow is governed by physical factors of hemodynamics.

Simplistically these are the same factors that are fundamental to an electrical current.
Ohm's law states the current (I) equals the voltage difference (ΔV) divided by resistance (R).
In hemodynamics, flow (Q) is equal to pressure difference (ΔP) divided by resistance (R).

Q = ΔP /R

Therefore

R (Resistance) = $\frac{\Delta \mathbf{P} \text{ (Change in Pressure)}}{\mathbf{Q} \text{ (Flow)}}$

Importantly resistance/(degree of VSM tone) is more important than pressure difference in influencing local blood flow.

Main effects of an increased arterial tone

- Decreased arteriolar radius.
- Increased resistance to flow.
- Potentially increased blood pressure.
- Decreased blood flow across involved segment.
- Decreased blood volume in capillaries.

Factors influencing resistance

Poiseuille's law applies to laminar flow.

$$\mathbf{R} = \frac{8 L \eta}{\pi r^4}$$

L = length of the vessel
η = viscosity of blood
r = radius of the vessel

Constant factors

- Blood vessel length – the longer the vessel, the greater the resistance encountered.

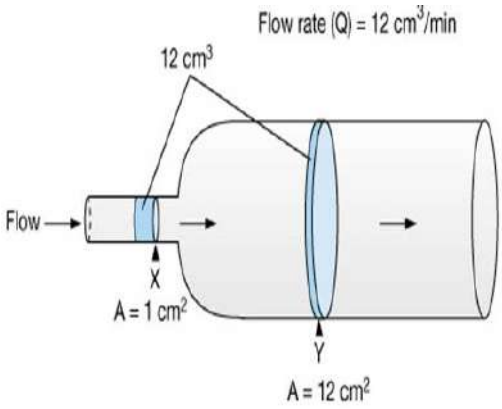
Dynamic Factors

- Blood vessel diameter
    - Changes in vessel diameter significantly alter peripheral resistance.
      Resistance varies inversely with the fourth power of vessel radius.
      For example, if the radius is doubled, the resistance is 1/16 as much.
- Blood viscosity – haematocrit, plasma proteins
- Turbulence (Reynolds equation help predict when this happens)
    - Acute branches
    - High velocity
    - Increased vessel diameter
    - Low viscosity

Blood Flow & Cross-Sectional Area

At the capillary bed:

- Vessel diameter decreases
- Number of vessels increase, increasing total cross-sectional area.
- Velocity slows down so that capillaries can unload O2 and nutrients.
- Majority of capillaries do not have vascular smooth muscle, therefore flow is determined by
    - Tone of the feeding arterioles and precapillary sphincters.
    - Other local factors for instance haematocrit, oxygen saturation of haemoglobin, functional activity nitric oxidase, endothelial factors, transmural pressure, etc.



Velocity (v) = Flow rate (Q) / Cross-sectional area (A)	
At point X	**At point Y**
$v = \frac{12\ cm^3/min}{1\ cm^2}$	$v = \frac{12\ cm^3/min}{12\ cm^2}$
v = 12 cm/min	v = 1 cm/min

The narrower the vessel, the faster the velocity of flow.

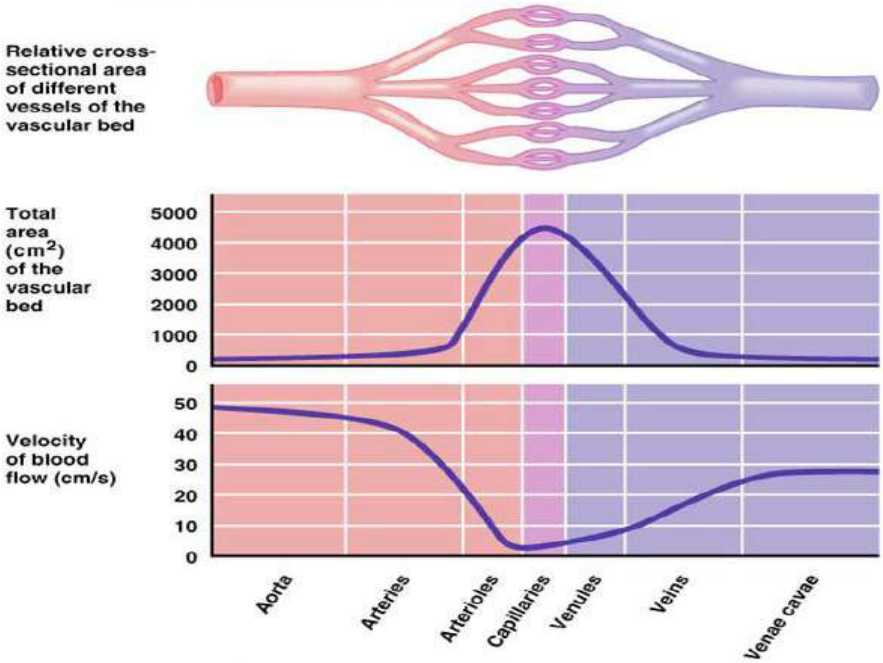


Image from Austin community college lecture on cardiovascular system
Image available from https://www.austincc.edu/apreview/PhysText/Vascular.html

Venous system

The venous system

- Contains roughly 70% of the blood volume.
- 30 times more complaint than the arterial system.

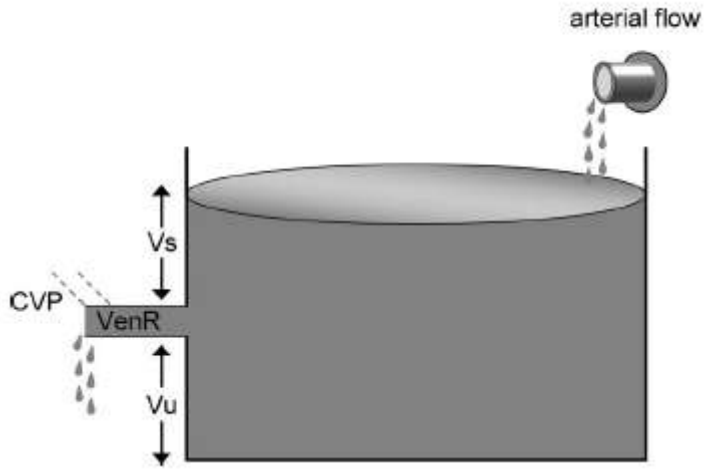
Capacitance vessels
Venous **capacitance** is the **volume of blood** contained within a vein at a certain **transmural pressure** (distending pressure or pressure inside versus outside the blood vessel).
Capacitance vessels serve as a reservoir that can easily change volume to maintain filling pressure in the right atrium.
Limb vessel are much less complaint than splanchnic vessels.
Cutaneous and splanchnic vessels are highly populated with α1 and α2 adrenergic receptors.

Capacitance = $\frac{\text{Volume}}{\text{Transmural pressure}}$

Compliance = $\frac{\text{Change in volume } (\Delta V)}{\text{Change in pressure } (\Delta P)}$

Splanchnic system (the main capacitance vessels in the body) receives 25% of the cardiac output and contains 20% of the blood volume.

Due to the high compliance of the venous system, changes in blood volume are associated with only small changes in venous transmural pressure.



Source: Figure 2 in Venous Function and Central Venous Pressure A Physiologic Story by Simon Gelman, M.D., Ph.D. Anesthesiology 2008; 108:735–48 the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

CVP = central venous pressure, **VenR** = venous resistance, **Vu** = unstressed volume, **Vs** = stressed volume.

Mean circulating filling pressure (MCFP)
Is the theoretical equilibration pressure in the circulatory system when the heart has stopped beating. The pressure is assumed to be mostly located in the venous capacitance vessels, particularly the splanchnic vasculature.
Understanding MCFP creates a conceptual framework for explaining how changes in venous reservoir compliance and capacitance are associated with alterations in CO when ventricular function is normal or minimally impaired.
Venous return is directly related to MCFP.
Effected by

- Venous capacitance
- Venous vascular compliance

$$\textbf{Venous return} = \frac{\textbf{MCFP – CVP(Central venous pressure)}}{\textbf{Venous resistance}}$$

Determinants of MCFP

- Mainly the stressed volume.
- And to smaller extent
    - Venous tone
    - Vascular pump
    - Functioning of valves.

MCFP is usually 7 – 12 mmHg where CVP is usually 3-5mmHg.

Stressed (Vs) versus unstressed volume (Vu)
The sum of the stressed volume (30%) and unstressed volume (70%) equals the total volume of blood in the venous system.

Stressed volume is the volume of blood in the vessel under transmural pressure above zero.

- Roughly 30% of predicted total blood volume (20-25 ml/kg)
- Is the hemodynamically active part/effective circulatory volume.

Unstressed volume is the volume of blood in the vessel under transmural pressure equal to zero.

- Blood volume required to fill the circulatory system to capacity without increasing cardiovascular transmural pressure.
- Composed of:
    - Recruitable volume (in **concept** similar the expiratory reserve volume in the lungs)
        - Able to recruit roughly 15-20ml/kg when maximally activated.

  - Residual volume (in **concept** similar to residual volume within the lungs)
- The recruitable volume can be mobilized into the stressed volume during time of need (Haemorrhage, trauma, etc)

Mechanism of recruiting volume from unstressed volume

- Venoconstrictors α1 change capacity but not compliance of the venous system.
  - Venous constriction only contributes 25% of total possible transfer of blood.
- During decreased flow into the splanchnic arteries, there is recruitment of blood out of the splanchnic venous capacitance system.
- Passive systems are more prominent in the splanchnic system and active systems more prominent in the liver.
- Example during aortic cross clamping proximal to celiac artery
  - There is a drastic decrease in splanchnic flow
  - Decrease in volume within the splanchnic veins (recruited from Vu).
  - Shift of the volume to the upper part of the body with an increase in VR and CO.

Venous Resistance

Venoconstriction of capacitance vessels

- Decreases the venous capacity.
- Expels blood from them into the systemic circulation.
- Causes increase in stressed volume and decrease in unstressed volume leading to increase in MCFP.
  - Increasing venous return (VR)
- Splanchnic system venoconstriction does not increase Venous Resistance.
  - It is outside the mainstream of blood flow to the heart through the vena cava.
- With severe activation of the alpha-adrenergic system in the hepatic vein and liver, there may be an increase venous resistance leading VR and CO to decrease.
- Importantly venous compliance is usually not affected.

Hypovolemia

Absolute and relative hypovolemia (decrease in Vs) trigger central and peripheral sympathetically mediated compensatory mechanisms.

Activation of alpha-1 receptors in the venous vasculature

- Decreases venous capacitance,
- Maintain venous return and CO by shifting blood from Vu to Vs.
- Helping maintain MCFP.

A compensatory decrease in splanchnic blood volume, for example, has been shown to increase Vs by as much as 10–15 mL/kg in haemorrhaged dogs due to decrease in venous capacitance and recruitment of Vu.

(Sepsis, acidosis, anaesthesia can impair the recruitment (redistribution) of blood from splanchnic and other blood.)

This helps explain why in a patient with 10-12% of blood volume loss, the hemodynamic values do not change significantly.

Decompensation can happen suddenly after the entire recruitable unstressed volume is fully mobilized.

Important to note that when mobilization of unstressed volume is driven by sympathetic stimulation, any intervention that decreases sympathetic outflow or venoconstriction (regional or general anaesthesia) outflow can cause rapid deterioration.

Interestingly venous capacitance vessels are much more sensitive to sympathetic stimulation than arterial resistance vessels.

- Small amount of increase in sympathetic tone leads to increased mobilization of blood from capacitance vessels without a significant increase in arterial resistance.
- With larger amount of sympathetic tone increase both increase mobilization of blood from capacitance vessels and increase in arterial resistance happen.

Resistance in splanchnic vessels

- Mainly located in hepatic veins and liver
- Mainly regulated by adrenergic receptors:

- Activation of α1 adrenergic receptors increases resistance.
- Activation of α_2-adrenergic receptors decrease it.
  - Leads to volume shift from the splanchnic vasculature into the systemic circulation.

During Normovolemia sympathetic stimulation shifts volume from the splanchnic vessels
During hypovolemia or severe sympathetic stimulation venous resistance can increase leading to sequestering of volume in the liver.

Role of Reflexes
When low blood pressure is sensed at the carotid sinus receptors or aortic baroreceptors:

- Increase in sympathetic tone,
- Constriction of splanchnic veins,
- Vs and thus MCFP increase,
- Increased venous return.

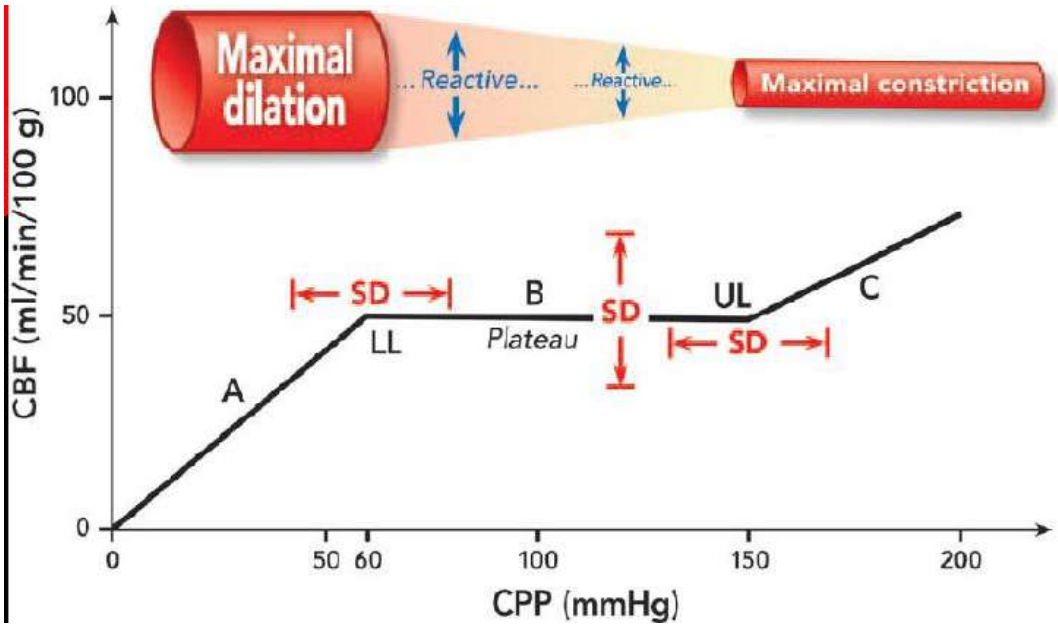
Venoarterial reflex
Increase in intravenous volume and associated distension of the vein leading to increases in arterial resistance (Less blood inflow into a vein leads to a decrease in intramural pressure and volume.)

Autoregulation (Not covered in depth)

Autoregulation of blood flow is the ability of an organ to maintain constant blood flow despite changes in perfusion pressure.
This is usually controlled by intrinsic mechanisms as described earlier.
Special areas in the body require tight control for optimal delivery of nutrients and oxygen and removal metabolic by-products.

CNS

Cerebral blood flow is not normally influenced by sympathetic nerve activity.
Maintains a constant blood flow in the normal range of arterial pressures.



Source: Neus Fabregas, Juan Fernández-Candil, (2016) in Complications in Neuroanesthesia,
Figure 1. Effect of hypercapnia on cerebral autoregulation
ISBN 978-0-12-804075-1 © 2016 Elsevier Inc. https://doi.org/10.1016/C2015-0-00811-5

Cerebral blood flow is regulated almost exclusively by **intrinsic** mechanisms:

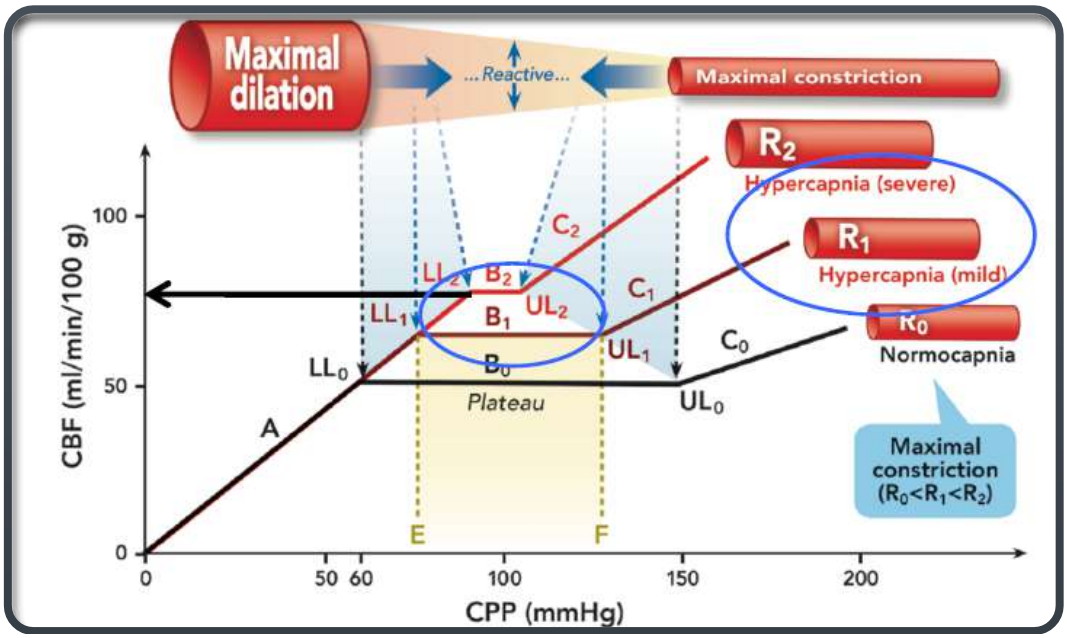
Myogenic:

- Dilate in response to decreased pressure.
- Cerebral arteries also sensitive to [$C0_2$].
- Dilate due to decreased pH of cerebrospinal fluid.

Metabolic:

- Sensitive to changes in metabolic activity.
- Areas of brain with high metabolic activity receive most blood.
- May be caused by [K^+].

Effect of CO2 on Cerebral blood flow (CBF) autoregulation



Source: Neus Fabregas, Juan Fernández-Candil, (2016) in Complications in Neuroanesthesia,
Figure 1. Effect of hypercapnia on cerebral autoregulation
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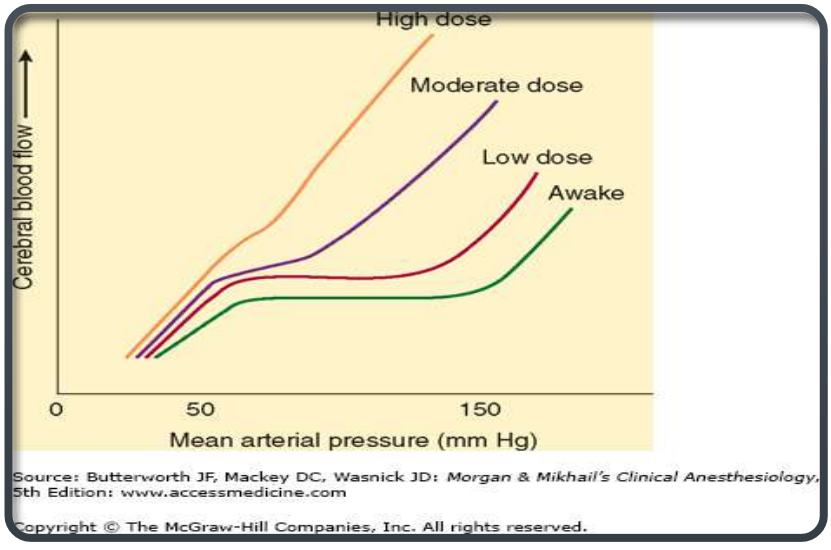
Autoregulation also susceptible to other influences or dysregulation:

- Trauma,
- Substances for instance volatile anaesthesia
- Diseased states for instance after a cerebrovascular event or chronic hypertension

Effect of Volatile anaesthetic on CBF autoregulation



Renal

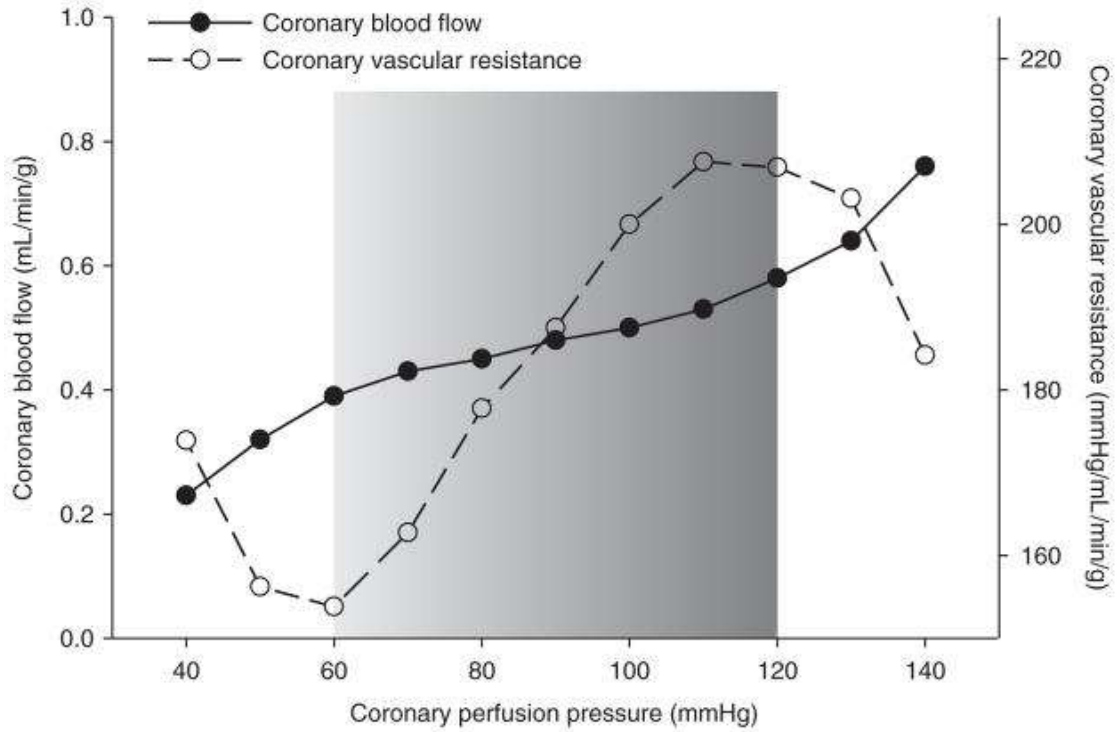
Autoregulation in the kidney allows for a near constant renal blood flow and glomerular filtration rate (GFR)
Two systems play a dominant role in renal vasculature autoregulation:

- Myogenic stretch of the preglomerular artery
  - Elevation in transmural pressure induce contraction of VSM.
- Tubuloglomerular feedback
  - Slower than myogenic stretch
  - Acts in conjunction with myogenic stretch
  - Senses the Na/Cl that reaches the macula densa in the distal tubule.

Coronaries

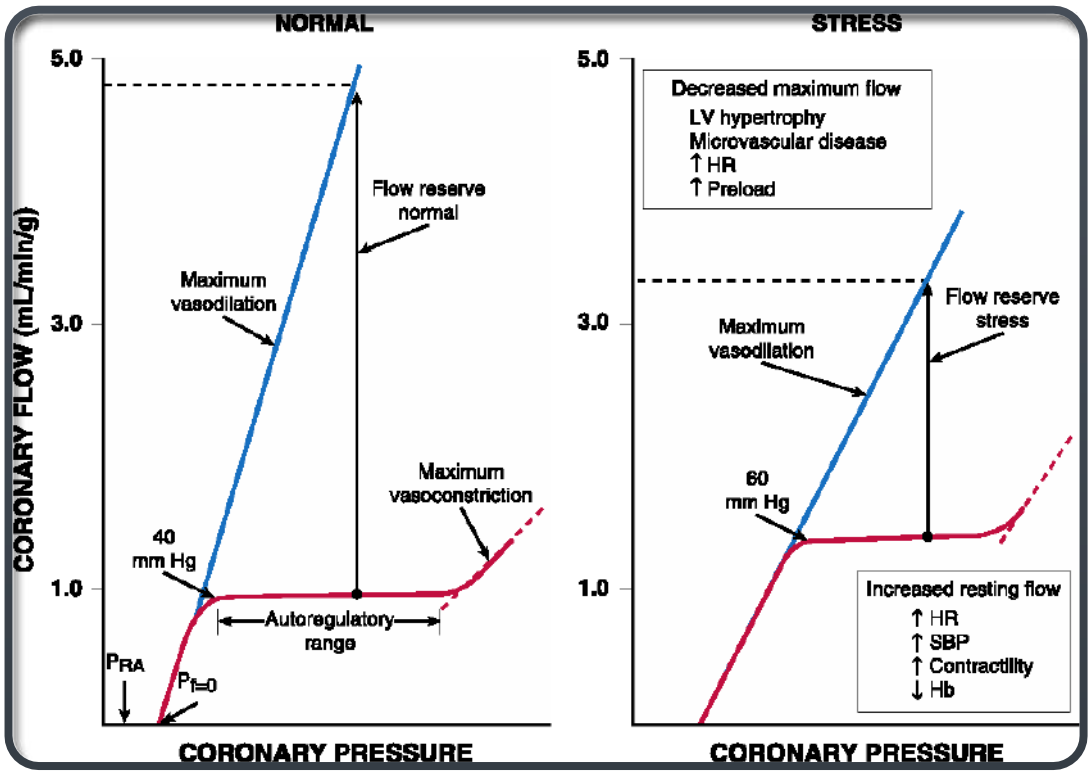
Regulation of coronary blood flow is dictated by multiple factors.

- Extravascular compressive tissue forces
  - Varies during the cardiac cycle and beat to beat.
- Intrinsic factor
  - Myogenic stretch
  - Local metabolic influences
  - Endothelial factors
  - Paracrine substances
- Extrinsic factors
  - Neurological
  - Hormonal influences



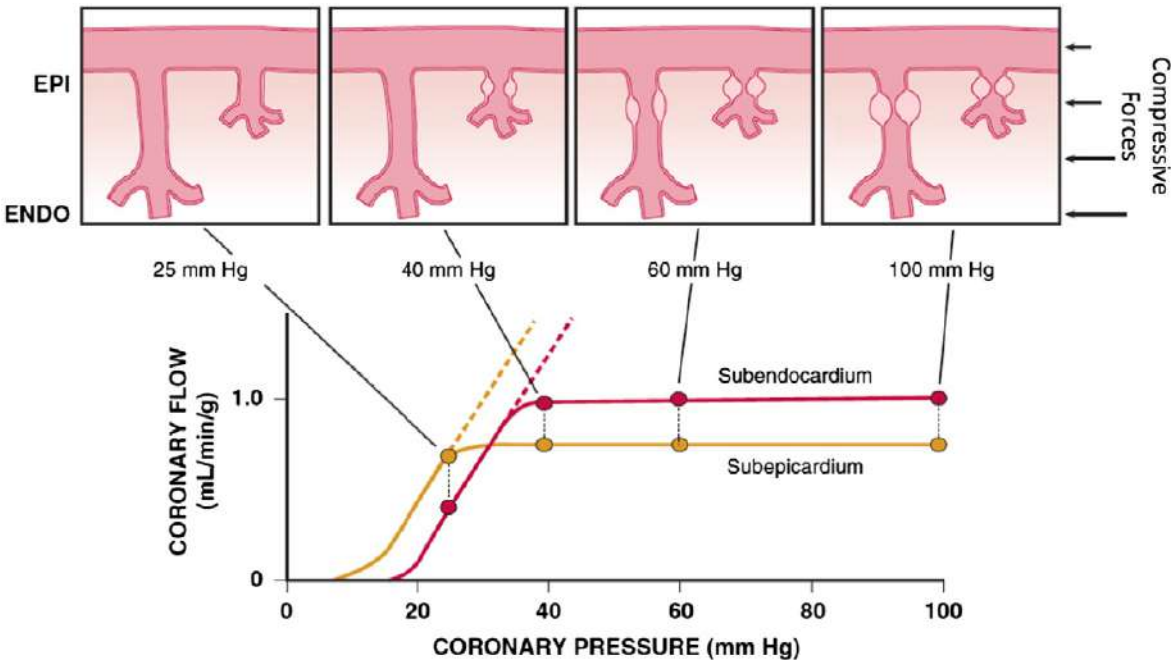
Source: Adam G. Goodwill,[1] Gregory M. Dick,[2] Alexander M. Kiel,[1,3] and Johnathan D. Tune published paper the Regulation of Coronary Blood Flow.
Figure 10 Relationship between coronary blood flow and coronary vascular resistance relative to coronary perfusion pressure
Compr Physiol. 2017 Mar 16; 7(2): 321–382.
Published online 2017 Mar 16. doi: 10.1002/cphy.c160016

Above figure illustrates the vascular smooth muscle tone change in relation to perfusion pressure in order to maintain a constant blood flow.



Source: D. Duncker, A. Koller, D. Merkus, J. Canty 2015 Published in Progress in cardiovascular diseases ***Regulation of coronary blood flow in health and ischemic heart disease.***
Fig 1 Autoregulatory relation under basal conditions and following metabolic stress.
DOI:10.1016/j.pcad.2014.12.002 Corpus ID: 3759966

Above figure illustrates the coronary blood flow autoregulation under normal and stressed situations



Source: D. Duncker, A. Koller, D. Merkus, J. Canty 2015 Published in Progress in cardiovascular diseases ***Regulation of coronary blood flow in health and ischemic heart disease.***
FIGURE 49-4 Transmural variations in coronary autoregulation and myocardial metabolism
DOI:10.1016/j.pcad.2014.12.002 Corpus ID: 3759966

Above figure illustrates the influences of external compressive forces in coronary autoregulation

Hypoxic pulmonary vasoconstriction (HPV)

HPV is the constriction of small intrapulmonary arteries in response to alveolar hypoxia.
Intrinsic mechanism matching ventilation and perfusion within the lung.

Optimizes systemic oxygen delivery and usually focal in nature but can be global spread throughout lung (High altitudes).

Usually, depending on the area undergoing HPV, blood is diverted from the hypoxic lung segment to a better-oxygenated portion of the lung without elevation of PAP.

Mechanism
Coordinated response of voltage and redox gated K^+ and Ca^+ channel triggered by a mitochondrial redox signal.

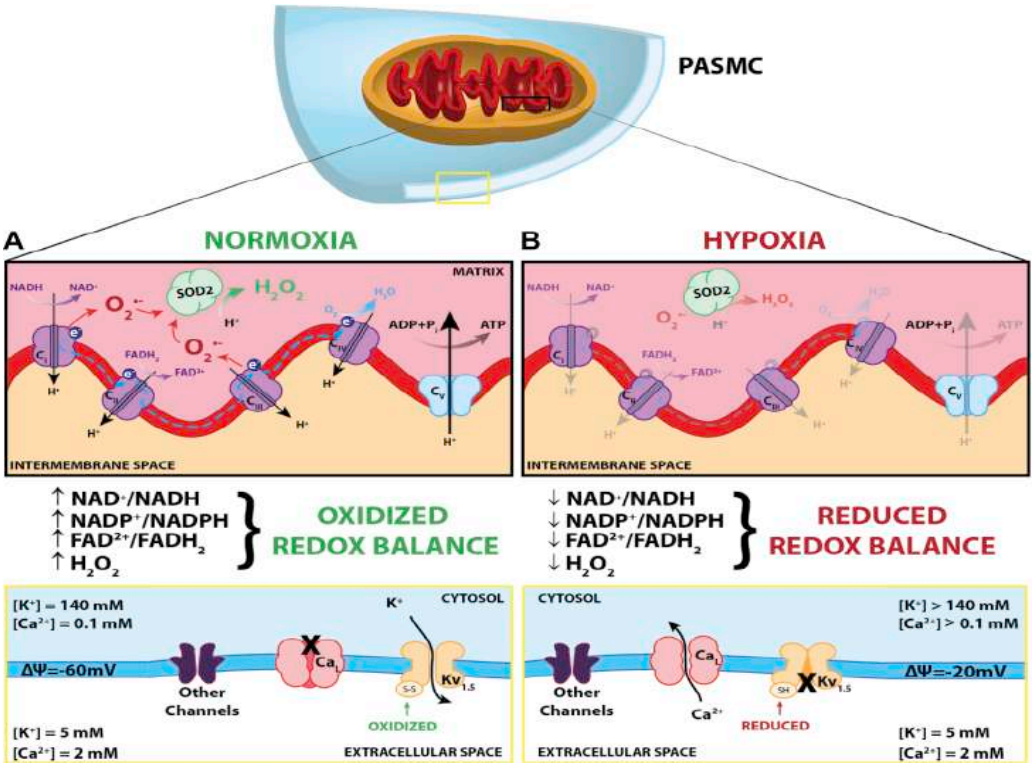
The core effector is pulmonary arterial smooth muscle cells (PASMC).

During hypoxia the mitochondrial redox state leads to the inactivation of voltage gated K^+ channels, which helps maintain resting membrane potential.

Due to the inactivation of these channels, the outward potassium current is decreased, which leads to an increase in resting membrane potential.

This in turn increases the opening-state probability of voltage gated L-type Ca channels causing an influx of Ca^+.

Activation of the PASMC follows, leading to vasoconstriction.



Source: Kimberly J. Dunham-Snary, PhD,[a] Danchen Wu, MD, PhD,[a] Edward A. Sykes, PhD,[a] Amar Thakrar, MD,[a] Leah R.G. Parlow,[a] Jeffrey D. Mewburn,[a] Joel L. Parlow, MD,[b] and Stephen L. Archer, MD[a,] from paper Hypoxic Pulmonary Vasoconstriction From Molecular Mechanisms to Medicine*
Published in Chest. 2017 Jan; 151(1): 181–192. Published online 2016 Sep 16. doi: 10.1016/j.chest.2016.09.001

Anaesthetic drug influence

Drug	HR	Arterial blood pressure	CO	Cardiac contractile force	MSP or MCFP	Vasomotor tone	Baroreceptor reflex activity	Sympathetic nerve activity	Splanchnic venous capacitance	Venous return
Inhalant anesthetic	↑↓±	↓↓	↓↓	↓	↓↓	↓↓	↓↓	↓↓	↑↑	↓↓
Injectable hypnotic										
Propofol	±↓	↓↓	↓	↓	↓	↓	↓	↓	↑↑	↓↓
Etomidate	±	↓	↓	↓	±↓	±↓	±↓	±↓	↑	±↓
Barbiturate	±↑	±	↓	↓	±↓	↓	↓	↓	↑	↓
Neurosteriod	±↓	↓	↓	±↓	±↓	±↓	↓	↓	↑	↓
Chloralose	↓	±	±	±	±	±	±	±	±	±
Dissociative										
Ketamine	↑	↑	↑±	↑±	--	--	--	--↑	--	--
Tiletamine	↑	↑	↑±	↑±	--	--	--	--↑	--	--
Opioid										
Morphine	↓	--↓	--↓	--↓	--	--	--↓	--↓	--	--↓
Hydromorphone	↓	--↓	--↓	--↓	--	--	--↓	--↓	--	--↓
Fentanyl	↓	--↓	--↓	--↓	--	--	--↓	--↓	--	--↓
Alpha-2 agonist	↓↓	↑→↓	↓↓	--↓	↑→↓	↑→↓	--↓	--	↓→↑	↑→↓
Benzodiazepine										
Diazepam Midazolam	--	--	--↓	--	--↓	--↓	--	--↓	--↓	--↓
Phenothiazine										
Acepromazine	±↓	↓	--↓	--↓	↓	↓	↓	↓	↑	↓
Local anesthetics										
Lidocaine	±↑	↓	--↓	--↓	↓	↓	--	↓	↑	↓
Bupivacaine	±↑	↓	--↓	--↓	↓	↓	--	↓	↑	↓

[a]Clinically relevant dosages are generally equal to or less than those recommended by the manufacturer. idealized effects expected from normal, healthy humans and animals; ↑, increase; ↓, decrease; ±, increase or decrease; --, little or no change; ↑→↓, increase followed by decrease; ↓→↑, decrease followed by increase. Data compiled from unpublished data (Muir WW, Del Rio CL, Ueyama Y. The effects of anesthetic drugs on mean circulatory filling pressure in isoflurane anesthetized dogs. (2015). Unpublished manuscript.) and (35, 39, 49, 51–53, 57, 61–78).

HR, heart rate; CO, cardiac output.

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Notes

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Temperature, thermodynamics and thermoelectrics

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University of Cape Town

Introduction

Temperature is the physical property of system that is perceived as the notion of “hot” or “cold”. Specifically, temperature is a fundamental property of matter. Temperature can be measured or quantified and for this purpose is described in terms of one of the seven basic SI units. The Kelvin is defined as 1/273.16 of the triple point of water.

Something that generally feels “hotter” has a higher temperature than something that feels “colder”. Should two objects be placed in contact, heat will move from the “hotter” to the “colder” object. If no net flow of heat occurs the objects are said to have the same temperature. The temperature is the result of the motion of the particles which make up a substance. Temperature increases as the motion of the particles increases.

Temperature is an intensive property of a system. It does not depend on the size of the system, the amount of matter, or the type of material in the system. This is the same as for pressure and density. In contrast, mass, volume, and entropy are all extensive properties, and depend on the amount of material in the system.

Two concepts are used in the description of temperature:

1. The thermodynamic concept
2. Statistical physics

Thermodynamics deals with the macroscopic measurement of temperature. The thermodynamic definition of temperature, first stated by Lord Kelvin, is stated entirely in terms of macroscopically measurable variables. This is the concept that we are most familiar with in the daily description of temperature.

Statistical physics provides an understanding of thermodynamics by describing matter as a collection of a large number of particles, and derives thermodynamic parameters as a statistical average of the microscopic parameters of the particles. In statistical physics the thermodynamic definition of temperature can be interpreted as a measure of the average energy in each degree of freedom of the particles in the system. For a solid, this energy is found primarily in the vibrations of its atoms around their equilibrium positions. In a mono-atomic gas, energy is found in the translational motion of the particles. Vibrational and rotational motions also provide thermodynamic degrees of freedom in liquids and poly-atomic gasses.

Heat

Heat is the process of energy transfer from one body or system to another due to thermal contact. Thermal contact is defined as an energy transfer to a body in any other way than due to work performed on the body.

Heat is a means of energy transfer, rather than a form of energy. Energy is transferred not heat!

The transfer of energy, through heat, can occur between objects as a result of radiation, conduction and convection. Evaporation is a combination of the above together with latent heat of vaporisation.

Temperature is used as a measure of the internal energy giving rise to heat transfer. The following definitions are used to describe the transfer of heat to objects:

1. Specific heat, or specific heat capacity, is defined as the amount of energy that has to be transferred to, or from, one unit of mass or mole of a substance to change its temperature by one degree. Units are Joules/kg/degree.

2. Heat capacity is the amount of energy required to raise the temperature of a given object by 1 degree. Units are Joules/degree.

3. Specific latent heat is the amount of energy required to convert 1 kg of a substance from one phase to another at a given temperature. Units are Joules.

The laws of thermodynamics

The laws of thermodynamics describe the transport of heat and work in thermodynamic processes. There are four laws of thermodynamics:

1. The Zeroth law of thermodynamics

   This law states that if two thermodynamic systems are each in thermal equilibrium with a third, then they are in thermal equilibrium with each other.

   When two systems are put in contact with each other, there will be a net exchange of energy between them, unless or until, they are in thermal equilibrium.

2. The First law of thermodynamics

   The first law states that energy cannot be created or destroyed. In an isolated system the total amount of energy remains the same. This law refers to the two ways that a closed system transfers energy to and from its surroundings – by the process of heating (or cooling) and the process of mechanical work. If energy is lost from one object it must be equal to that gained by another.

3. The Second law of thermodynamics

   This law states that systems containing energy have a tendency to increase their entropy rather than decrease it. Simplistically heat will flow from a higher temperature region to a lower temperature region, but not the other way around.

4. The Third law of thermodynamics

   This law states that as temperature approaches absolute zero, the entropy of a system approaches a constant minimum. This law postulates that entropy is temperature dependent and results in the formulation of the concept of absolute zero.

The measurement of temperature

Temperature is measured with thermometers that can be calibrated to a variety of scales. The scientific world measures temperature using the Celsius scale, and thermodynamic temperature using the Kelvin scale. The word thermometer is derived from the Greek *thermo* meaning “warm” and *meter* meaning “to measure”.

The basic unit of temperature (symbol T) in the SI system is the Kelvin (symbol K). The Kelvin and Celsius scales are by international convention defined by two points:

1. Absolute zero
2. The triple point of Vienna standard mean ocean water. (This is water prepared with specific isotopes of hydrogen and oxygen.)

Absolute zero is defined as being precisely 0K and -273.15^{0}C. Absolute zero is when all kinetic motion in the particles comprising matter ceases and they are at complete rest in the classic sense. At absolute zero matter contains no thermal energy.

The triple point of water is defined as being precisely 273.16 K and 0.01^0C. This definition does three things:

1. It fixes the magnitude of the Kelvin as being 1 part in 273.16 parts
2. It establishes that one Kelvin has exactly the same magnitude as one Celsius.
3. It establishes the difference between the two scales' zero points as exactly 273.15 Kelvin.

In the field of plasma physics, because of the high temperatures and the electromagnetic nature of the phenomena, it is customary to express temperature in electron Volts (eV) or kiloelectronVolts (keV), where 1 eV= 11.604 K

For everyday applications the Celsius scale is used. 0^0C corresponds to the freezing point of water and 100^0C to the boiling point of water at sea-level. In this scale a temperature difference of 1 degree is the same on both the Celsius and Kelvin scales. The scales are the same apart from being offset by 273.15 degrees.

In the USA the Fahrenheit scale is widely used. On this scale the freezing point of water is 32^0F and the boiling point 212^0F.

It is not generally convenient to place objects in contact with one another to see if a transfer of heat energy occurs (zeroth law of thermodynamics) therefore it is useful to establish a reference device. The device can be calibrated based on the properties of a reference system and used to measure the temperature of other systems.

The gas thermometer

One such reference system is a fixed quantity of gas. The ideal gas law states that the product of the pressure and volume of a gas is directly proportional to the temperature.

$$P.V = n.R.T$$

T is the temperature, n the number of moles of gas and R the gas constant. One can define a scale for temperature based on the corresponding pressure and volume of the gas. The temperature in Kelvin is the pressure in Pascals of one mole of gas in a container one cubic meter, divided by 8.31. A gas thermometer is not very convenient, but other instruments can be calibrated to its scale.

From a practical perspective a gas thermometer cannot be used to measure absolute zero since all gasses will condense prior to reaching such a low temperature. Nevertheless, the gas thermometer has been used practically, for the calibration of thermometers used in every-day life.

The temperature of an ideal gas is related to its average kinetic energy via the equation below.

$$Ek = \frac{3}{2}\kappa T$$

K is equal to R/n (the ideal gas constant divided by the number of mole).

Other thermometers

As the gas thermometer is not practical, we make use of a variety of other measuring instruments.

Thermometers can be classified as:

1. Primary thermometers
2. Secondary thermometers

Primary thermometers

For primary thermometers the measured property of matter is known so well that temperature can be calculated without any unknown quantities. Examples of these are thermometers based on the equation of the state of a gas, on the velocity of sound in a gas, on the thermal noise voltage or current of an electrical resistor, and on the angular anisotropy of gamma ray emission of certain radioactive nuclei in a magnetic field. As you would realise, primary thermometers are relatively complex and unsuitable for use in the clinical environment.

Secondary thermometers

Secondary thermometers are most widely used because of their convenience. For secondary thermometers, knowledge of the measured property is not sufficient to allow direct calculation of temperature. These instruments have to be calibrated against a primary thermometer.

The standard for calibration of secondary thermometers has been as follows:

1. Immerse the sensing portion in a stirred mixture of pure ice and water at 1 standard atmosphere, and mark the point of thermal equilibrium
2. Immerse the sensing portion in a steam bath at 1 standard atmosphere and again mark the point of thermal equilibrium
3. Divide the distance between the marks into equal portions according to the temperature scale being used

As most of the thermometers in every day use are secondary thermometers we can classify these as follows:

Direct measuring instruments

1. Liquid expansion thermometers – either alcohol or mercury based
2. Dial thermometers – a volatile liquid in a bulb is attached to a Bourdon-type pressure gauge
3. Bimetallic strip thermometers – 2 different metal strips with different coefficients of expansion are connected to a needle on a gauge
4. Chemical thermometers – liquid crystal changes colour at different temperature

Indirect measuring instruments

1. Resistance wire thermometers – platinum is most often used. Resistance is directly related to temperature. These thermometers characteristically have a long stabilisation time and are thus not often used.

2. Thermistor thermometers – Co, Mn, Ni oxides are frequently used.

   Thermistors work on the principle of a change (non-linear) in resistance with temperature. A thermistor is a type of resistor whose resistance varies with temperature. Thermistors differ from resistance temperature detectors (RTD) in that the material used in a thermistor is generally a ceramic or polymer, while RTDs use pure metals. The temperature response is also different; RTDs are useful over larger temperature ranges, while thermistors typically achieve a higher precision within a limited temperature range.

3. Thermocouple thermometers – These make use of the Seebeck effect (described later)
4. Crystal resonators – the resonance frequency of crystals is temperature dependent
5. Transistor detector thermometers
6. Wire thin film thermometers
7. Infrared thermometers

   These have found increasing application in the clinical environment, particularly with respect to the measurement of tympanic temperature. The detector is a thermopile that responds to infrared radiation from the tympanic membrane.

To understand the workings of many of the indirect measuring instruments we need to look for an understanding of thermoelectrics.

Thermoelectrics

The thermoelectric effect is the direct conversion of temperature differences to electric voltage (potential difference) and vice versa. A thermoelectric device creates a voltage when there is a temperature difference on each side of it. When a potential difference is applied to a thermoelectric device, it will create a temperature difference on either side of it.

The effect described above can be used to measure temperature, generate electricity, cool objects or heat them.

The term thermoelectrics encompasses three separate effects:

1. The Seebeck effect
2. The Peltier effect
3. The Thomson effect

And one additional concept:

4. Joule heating

The Seebeck effect

Seebeck discovered that a compass needle would be deflected when a closed loop was formed of two metals joined in two places with a temperature difference between the junctions. The reason for this is the induction of current and the generation of a magnetic field, related to the way the two metals respond to the temperature difference. Seebeck did not recognise that an electric current was involved and incorrectly termed it the thermomagnetic effect. He thought the two metals became magnetically polarised by the temperature difference.

The effect is that a voltage, the thermoelectric EMF, is generated in the presence of a temperature difference between two different metals or semiconductors. This causes a continuous current to flow in the conductors if they form a complete loop. The potential difference created is in the order of several microvolts per degree difference. The thermoelectric power of the circuit is related to the thermoelectric power of the metals (the Seebeck coefficients) in much the same way as half-cell potentials contribute to overall EMF in an electric battery. The Seebeck coefficients are non-linear as a function of temperature and depend on the conductor's absolute temperature, material and molecular structure.

The Seebeck effect is commonly used in a device called the thermocouple. This can be used to measure a temperature difference directly, or to measure an absolute temperature when one end of is set to a known temperature. Several thermocouples can be connected to create a thermopile. A thermopile has a greater voltage output than the individual output of each thermocouple. Consider this analogous to the connection of many battery cells in series.

The Peltier effect

In contrast to the Seebeck effect described above, when a current is made to flow through a circuit of two dissimilar metals, heat is absorbed at one junction and evolved at the other. The individual couples can be connected in series to enhance the effect.

An interesting consequence of this effect is that the direction of heat transfer in controlled by the polarity of the current. Reversing the polarity will change the direction of heat transfer.

The Thomson effect

Any current carrying conductor (except for superconductors), with a temperature difference between two points, will either absorb or emit heat, depending on the material.

In metals such as zinc and copper, which have a hotter end at a higher potential and a cooler end at a lower potential, when current moves from the hotter end to the cooler end, it is moving from a high to a low potential, so there is an evolution of heat. This is called the positive Thomson effect.

In metals such as cobalt, nickel and iron, which have a cooler end at a higher potential and a hotter end at a lower potential, when current moves from the hotter end to the colder end, it is moving from a low to a high potential, there is absorption of heat. This is called the negative Thomson effect.

Joule heating

This is also known as resistive heating or Ohmic heating. This is the process by which the passage of an electric current through a conductor releases heat. The heat produced is proportional to the square of the current multiplied by the electrical resistance of the wire.

$$Q \alpha I^2 . R$$

The above relationship is known as Joule's first law. The SI unit of energy was subsequently named the joule and given the symbol J. The commonly known unit of power, the watt, is equivalent to one joule per second. It is important to appreciate that the higher the current flow the greater the amount of joule heating. It is for this reason that electricity supply is based on higher voltage and lower current flow.

Joule heating can be obviated through the use of superconductors.

Summary

This refresher course has dealt specifically with the physical aspects of temperature and its associated concepts. The notions of temperature and heat have been discussed and defined. The laws of thermodynamics have been stated and the application of these with respect to the measurement of temperature highlighted. Thermometers used for the measurement of temperature have been classified.

Lastly the important concepts in thermoelectrics have been highlighted.

References

As additional preparation I suggest the following:

1. Clinical temperature measurement. Colin Clinton, FCA I refresher 1996.
2.Temperature – physiology and measurement. Pieter du Toit, FCA I refresher 2001.
3.Temperature and anaesthesia. Howard Radford, FCA I refresher 2004.
4.Temperature and humidity – physics, measurement and clinical application. Peter Gordon, FCA I refresher 2009.

Notes

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Electricity
A brief review

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What will be covered:

- Basic concepts of electricity and magnetism
- Electrical voltage, AC and DC current, resistance, impedance
- Electrical circuits: series and parallel
- Symbols of basic components of electrical circuits
- Capacitance, inductance
- Wheatstone bridge: principles, usage
- Electrical hazards: causes and prevention.
- Electrocution: including microshock, earth faults, leakage
- Electrical equipment safety: domestic and medical, classification/ types of equipment, symbols
- Circuit breakers, fuses
- Transformers, inductance
- Transistors, diodes
- Amplifiers: band width, low pass, high pass, band pass filters
- Defibrillators and defibrillation: principles, including thoracic impedance, monophasic, multiphasic, implantable devices.
- Diathermy: monopolar, bipolar; safety and uses

Learning outcomes:

- Be able to define key concepts and units of measurement relating to electricity.
- Understand the relationship between current, voltage and resistance.
- Explain the principles of resistors and how they are used in a Wheatstone bridge.
- Explain the principles of capacitors.
- Have a basic understanding of electromagnetism and inductance to explain the principles of inductors and transformers.
- Understand how diodes and transistors work.
- Understand the principles of amplifiers and how they may be used as filters.
- Explain how electricity is supplied.
- Discuss the potential hazards of electricity and how they may be prevented.
- Understand the danger of electrocution.
- Describe electrical equipment, safety equipment, and how they may be used.
- Describe the additional electrical safety methods of earthing, fuses, circuit breakers, and floating circuits.
- Understand the principles of diathermy, the potential risks and how these may be minimised.

ELECTRICITY CONCEPTS:

- Basic concepts of electricity
- Electrical voltage, AC and DC current, resistance, impedance
- Electrical circuits: series and parallel

Charge (Q)

- Electric charge is the physical property of matter to experience a force when it is in the proximity of other charged matter.
- Unit of measurement: coulombs
- 1 coulomb (C)
    - amount of charge passing any single point in a circuit within 1 second when a current of 1 ampere is flowing.
    - equivalent to the charge carried by 6.242×10^{18} electrons.
- Charge moves from an area of high charge density, or potential, to an area of lower charge density.

Conductor

- Material that allows the passage of electrical current.
- Often a material with loosely bound electrons in atoms' outer shells e.g., metals, carbon.
- Charged ions within a solution, e.g., body fluids.

Insulator

- Material that will not conduct electricity under any conditions.
- Electrons in outer shell of atoms tightly bound.
- E.g., plastic, rubber, glass

Semi-conductor

- Material with conductivity in between an insulator and a conductor
- Conducts electricity under certain conditions, e.g., temperature.
- ↑ temperature = ↓ resistance
- Usually silicon-based
- Doping: addition of an impurity to improve conductivity, e.g., adding phosphorus to silicon.
- Uses: diodes, thermistors, transistors

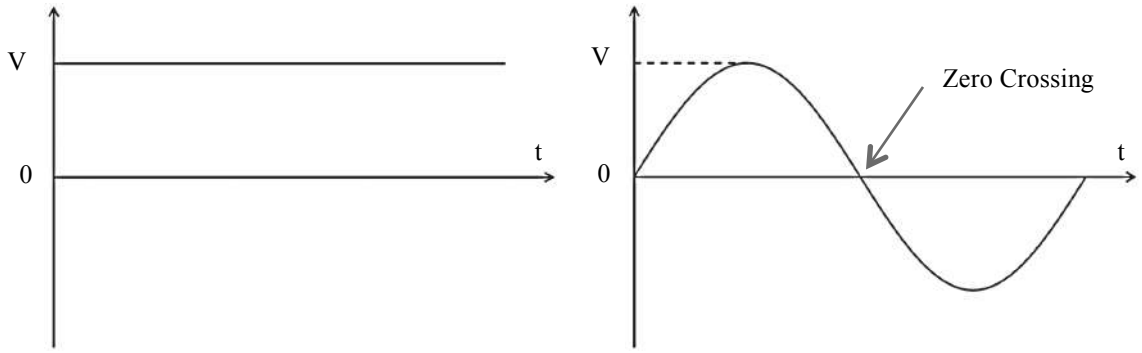
Current (I)

- The rate of flow of electrical charge past a point in a circuit
- Unit of measurement: amperes (A)
- "1 ampere is the amount of current producing a force of 2×10^{-7} Newtons/metre between two indefinitely long parallel conductors placed 1m apart in a vacuum."

Voltage (V)

- The potential 'energy' available to drive the flow of electrons.
- Potential, potential difference and electromotive force are all terms that may be used when describing voltage.
- The potential of any point is the voltage of that point above zero (earth)
- Unit of measurement: volts (V)
- "1 volt is the difference of electrical potential between two points of a conductor carrying 1A of current, when the power dissipated between the points is 1 watt."

DC vs AC



Direct Current Alternating Current

- *Direct current:*
  - steady flow of current from positive to negative (electrons move in opposite direction to current)

- *Alternating current:*
  - Oscillating flow of current
  - Produced as potential changes.
  - Oscillates at a frequency- SA mains = 50 Hz

Resistance (R)

- Opposition to the flow of electrical current, causing a drop in potential difference (voltage).
- Unit of measurement: ohms (Ω)
- "1 ohm is the resistance that will allow 1A of current to flow through a material when a potential of 1V is applied across it."
- Resistance of a material may depend on the physical stresses to which it is subjected.

Ohm's Law

- $Current\ (I) = \frac{V}{R}$

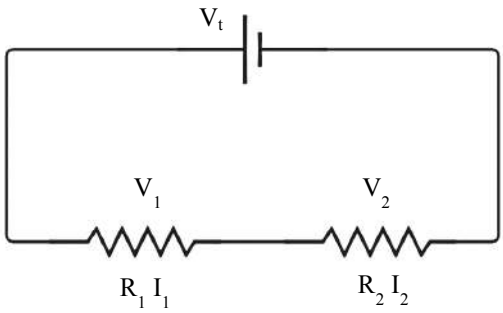
Reactance (X)

- Opposition to the flow of circulating current.
- Due to inductance and capacitance
- ↑AC frequency = ↓reactance
- Unit of measurement: ohms (Ω)

Impedance (Z)

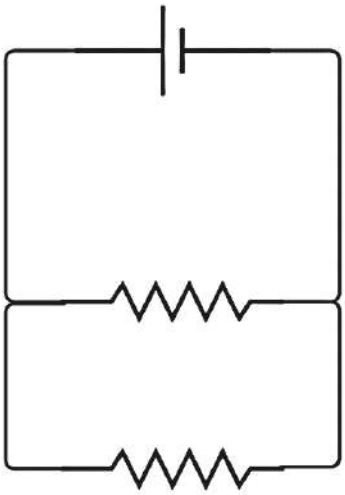
- Total opposition to the flow of alternating current
- Combines resistance and reactance.
- Unit of measurement: ohms (Ω)
- Has a magnitude and a phase.

Series Circuits



- Components placed one after another.
- Electrical current passes through all components so any breaks = no flow of current
- Current is constant throughout:
  $I_{total} = I_1 = I_2$
- Circuit resistance is the sum of the resistances of all components:
  $R_{total} = R_1 + R_2$
- Circuit voltage is the sum of all voltage within the circuit:
  $V_{total} = V_1 + V_2$

Parallel Circuits



- Circuits that contain branches
- Multiple branches may arise from a single junction.
- Branch must re-join main circuit for current to flow in that branch- current still flows through remainder of circuit if breaks in individual branches.
- Current in individual branches inversely proportional to branch resistance.
- Circuit current is the sum of the current in each branch:
  $I_{total} = I_1 + I_2$
- Circuit resistance is lowered by branching:
  $1/R_{total} = 1/R_1 + 1/R_2$
- Voltage in all branches is equal:
  $V_1 = V_2$

BASIC ELECTRICAL COMPONENTS:

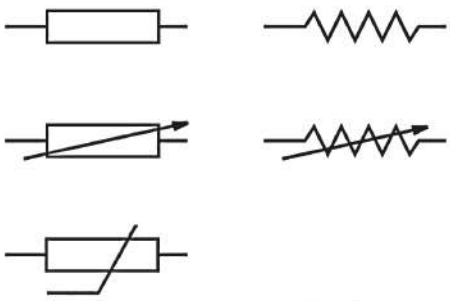
- Symbols of basic components of electrical circuits
- Wheatstone bridge: principles
- Capacitance

Battery

Cell Battery

- Group of galvanic cells storing chemical energy- released as electrical energy.
- Each cell = negative cathode and positive anode connected by conductive electrolyte
- Anode oxidation + cathode reduction = flow of electrons

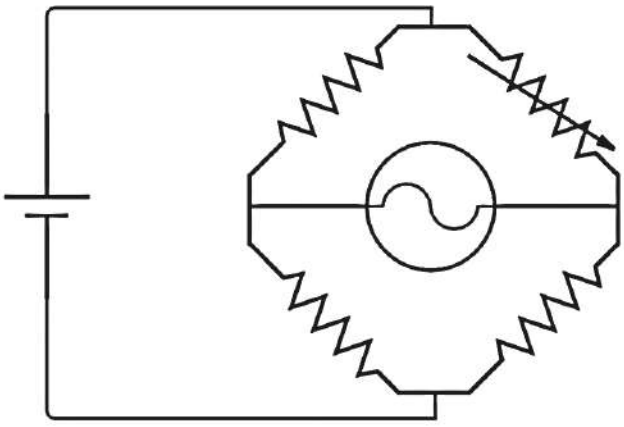
Resistors



- A component that restricts the flow of electrical current.
- *Fixed resistor:* set resistance.
- *Variable resistor:* changeable resistance
- *Thermistor:* resistance dependent on temperature
  - Low temperature = high resistance

Wheatstone bridge

- Classically found in arterial line monitoring
- Allows accurate measurement of small value changes.
- Voltage divider circuit, with null deflection galvanometer
- No difference in potential (voltage) between branches = balanced (galvanometer=0)



$$\frac{R_1}{R_2} = \frac{R_3}{R_4}$$

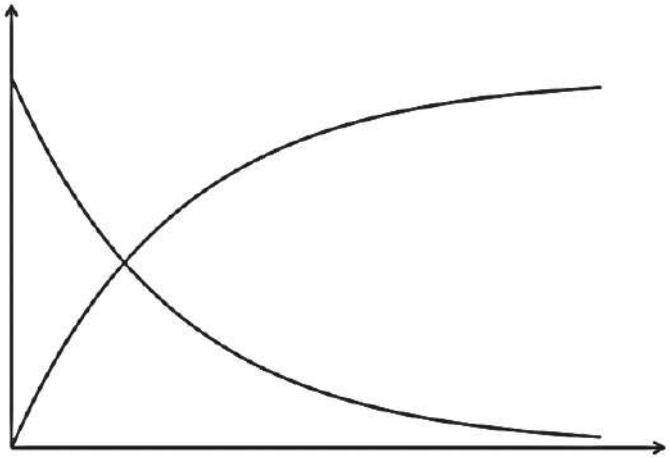
Capacitance

- The ability to store electrical charge.
- Unit of measurement: farads (F)
- "1 Farad is the capacity of an object to store 1 coulomb of charge when a potential difference of 1 volt is applied to it."

Capacitor

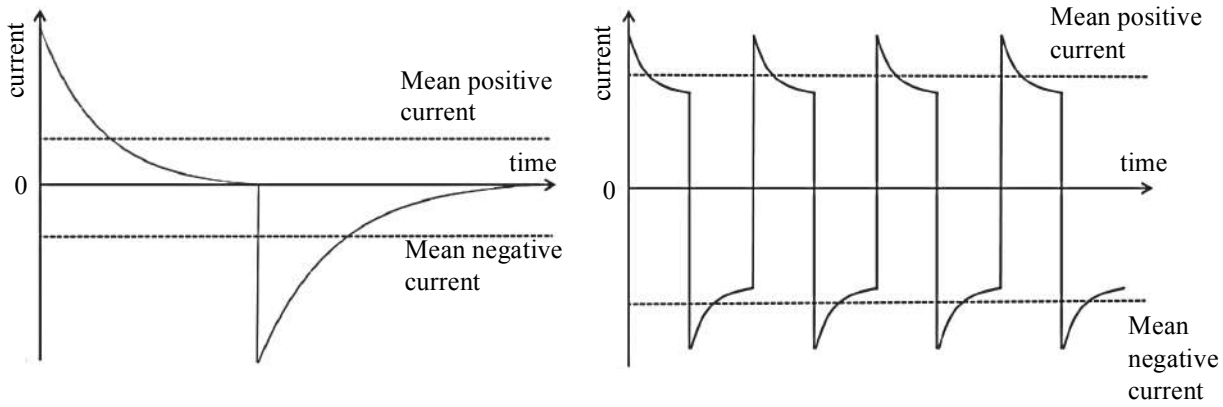
- Component that stores electrical charge
- Two conducting plates separated by non-conducting dielectric material.
- Capacity depends on:
  - Size of plates
  - Size of separation gap
  - Dielectric material
- Used in defibrillators and filters.
- Plate becomes negatively charged by electrons → electrons driven off other plate due to repulsion.
- Once capacitor fully charged, current flow in circuit stops- rate of decay of current=exponential
- If full, current can only continue if polarity reversed.
- Preferentially allows flow of AC over DC (has high resistance but low reactance), with high frequency AC passing most easily- act as low frequency filters.
- Energy stored by capacitor:
  - $E = ½ QV$
  - $E = ½ CV^2$

***Capacitor in DC circuit**:*



Capacitor in AC circuit:

Capacitor in low frequency AC circuit *Capacitor in high frequency AC circuit*



Higher frequency = less time for current decay = greater mean current flow

ELECTROMAGNETISM AND INDUCTANCE:

Electromagnetism

- Current flowing through conductors generates magnetic fields.
- Magnetism: current flowing through a conductor exerts a force on another conductor.
- Ferromagnetic material: electrons generate small currents → magnetic fields.
- If conductor exposed to varying magnetic field, potential difference created within conductor- electromotive force.

Inductance

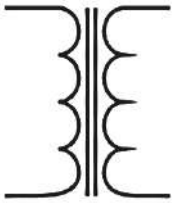
- Generation of electromotive force (EMF) in opposition to a changing current
- Changing current → changing magnetic field = magnetic flux
- Faraday's Law of Induction: induced EMF in a circuit proportional to the rate of change over time of the magnetic flux through that circuit
- Unit of measurement: henry (H)
- "1 henry is the inductance when 1A flowing through the coil generates a magnetic field strength of 1 weber."
- Source of electrical interference

Inductor

- Generates electromotive force to oppose changes in current flow.
- Made of a coil of wire, may have a ferromagnetic metal core.
- Induced electromotive force proportional to the rate of change of current.
    - High frequency current = ↑ EMF (high frequency filter)
    - DC and low frequency AC pass more easily
- Used in defibrillator to slow the flow of current → smooths and lengthens current pulse.

Transformer

- Transfer energy from one circuit to another
- Two inductor coils (primary and secondary0 wound around the same core (former)
- AC in coil 1 (primary) = magnetic flux in core = induced current in coil 2 (secondary)
- No conductive connection between the two circuits

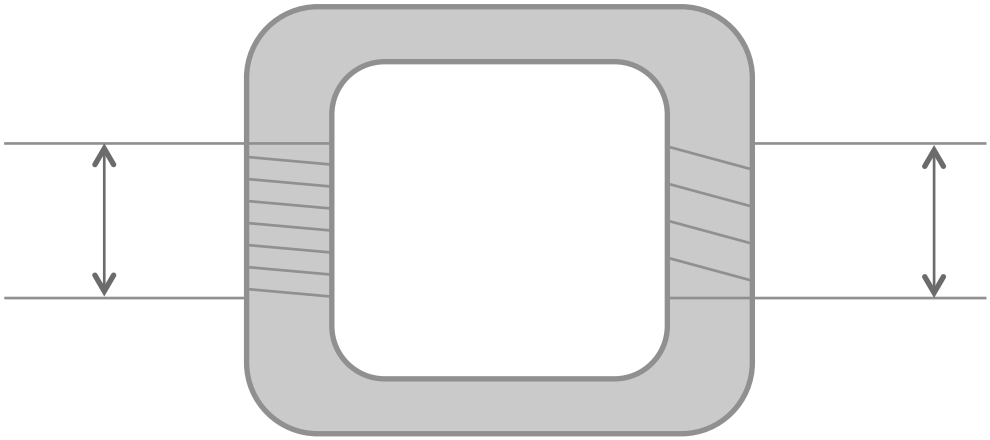


Step transformers

- Number of turns in each coil affects the voltage generated.
- Step up = increases voltage
  - Turns in primary coil < turns in secondary coil.
  - Used to make voltage more suitable for transmission through power lines over long distances.
- Step down = reduces voltage
  - Turns in primary coil > turns in secondary coil.
  - Used to make voltage a lower level, suitable for domestic use.

Transformer equation

- Derived from Faraday's Law of Induction
- $V_p/V_s = N_p/N_s$



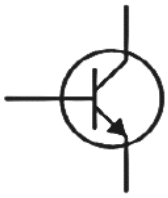
Isolation transformers

- Isolate part of the internal electronics of a device from the power supply
- Step transformers or deliver same voltage
- Improve safety as decreased risk of electric shock
- May also protect sensitive components from power surges or minimise electrical interference

FURTHER ELECTRICAL COMPONENTS:

Transistors

- Semiconductor device
- Electronic 'gate" used to control the flow of current
- Three (or more) electrical connections:
  - Two form the path of current
  - One controls the flow of current



Diode

- Also known as a rectifier
- Allows current to flow in one direction only
- May be used to convert AC → DC

- LED: light-emitting diode

Amplifiers

- Increase the size of a signal to facilitate interpretation.
- Electrical or non-electrical
- Used widely in patient monitoring.
- Gain:
    - Amount by which the signal is amplified.
    - Unit of measurement: bels (decibels)
- Noise:
    - Amplified unwanted signals.
    - Amount of noise in relation to desired output= signal to noise ratio
- Bandwidth:
    - Range of frequencies amplifier works reliably across

Amplifiers as filters

- Differential amplifiers- use common mode rejection.
- Bandwidth amplifiers- only amplify a set frequency range.
- High pass filters- only allow signals above a set frequency.
- Low pass filters- only allow signals below a set frequency.
- Notch filters- reject signals of a set frequency.
- Specific amplitude filters

ELECTRICITY SUPPLY:

- Basic concepts
- Electrical hazards: causes
- Electrical equipment safety: domestic
- Fuses

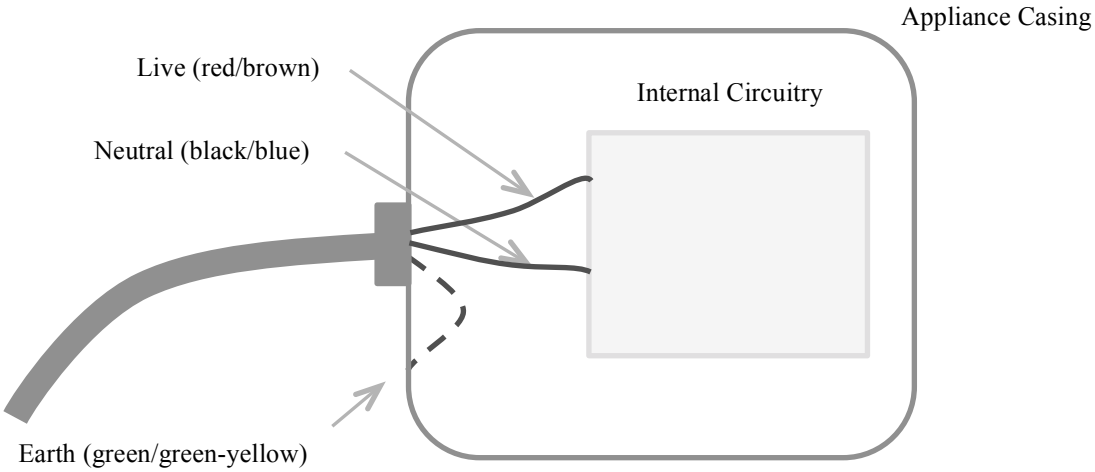
Mains electricity supply

- Generated using electromagnetic induction.
- Alternating current with a frequency of 50Hz at 230V (root mean square voltage)
- RMS voltage= peak voltage/$\sqrt{2}$
- Transmission of AC via high voltage pylon network (≈400,000V)

- Power lost as heat during transmission: $P = I^2R$
    - Maximise voltage to minimise current = ↑ efficiency

Domestic supply

- SA appliances = 3 wires:
    - Live- carries charge to appliance.
    - Neutral- return to source
    - Earth- connects to ground.



Fuses

- Small glass/ ceramic canisters containing thin wire
- Placed on the live wire in the plug
- In the event of an electrical fault:
    - Appliance casing and earth wire have low resistance
    - Higher current is drawn from the supply → heat melts fuse wire → circuit broken
- Fuses are rated in amperes, which is the current that will melt the fuse wire

Hazards of electricity

- Electrocution
- Burns
- Interference with monitoring
- Fire/explosion
- Electrical failure

<u>Electrocution:</u>

- Electrical hazards: causes
- Electrocution: including microshock, earth faults, leakage.

Hazards of electrocution

- Electrocution occurs when current passes along an unintended path.
- Damages tissues or causes electrophysiological abnormalities.
- Resistive coupling:
    - Direct physical contacts between source, person, and earth
    - Causes: faults, leakage currents
- Capacitive coupling:
    - Person acts as plate of capacitor- no direct connection with source.

Electrocution effects depend on:

- How much current flows
- Type of current
- Current pathway
- Current density
- Duration of current flow

Current magnitude and type

- Amount of current determined by Ohm's law (I=V/R)
- Power dissipated: $P=I^2R$
- Person provides lower resistance path so more current flows → ↑ power = ↑ tissue damage
- AC more harmful than DC;
    - DC = single muscle contraction
    - AC = tetany ('can't-let-go')- peak effect @ 50Hz
    - High frequencies (>1000Hz) less likely to cause damage.

Current path, density and duration

- Path electricity takes determines harm done.
    - Cardiac muscle; ventricular fibrillation
    - Chest wall: respiratory muscle tetany and asphyxiation
    - CNS: spinal cord damage and loss of consciousness
- Current density- amount of current flowing per unit cross-sectional area of a material
    - ↑ current density = ↑ damage
    - If wider tissue cross-sectional area, pathway of the electricity broader, so the amount of electrical current individual tissues in area exposed to is lower.
- ↑ Current duration = ↑ damage
    - If a lower current density is experienced for a sustained period of time, then significant damage can still occur.
    - If electrocution is very brief, then higher current is required to cause damage.

Physical effects of electrocution

- 1-5 mA: tingling sensation
- 5-10 mA: ain
- 15 mA: 'can't-let-go' threshold
- 50 mA: respiratory arrest, arrhythmias
- 100 mA: VF

- Burns:
    - Depends on current density and tissue impedance.
    - Dry skin = ↑ impedance so burns mostly at entrance and exit points

Impedance

- Current = voltage/impedance
- Impedance values:
    - Skin = 2,000 Ω
    - Body tissues = 500 Ω
    - Shoe soles = 200,000 Ω
- A barefoot person electrocuted with mains AC:
    - Current = 230/4,500 = 51 mA
    - Respiratory arrest and arrhythmia
- A person wearing shoes electrocuted with mains AC:
    - Current = 230/204,500 = 1.1 mA
    - Mild tingling

Microshock

- Occurs when skin breached and current applied directly or in very close proximity to the myocardium
- Higher current density generated at the myocardium so much lower current able to cause damage (as low as 100 μA can cause dangerous dysrrhythmias under these circumstances)
- Harm unlikely if the microshock delivered <44 μA
- Leakage currents transmitted via PA catheters/central lines/pacing wires are able to cause significant harm
- Risk of significant ventricular arrhythmia:
    - Depends on site of stimulation (ventricles more sensitive to microshock)
    - Proportional to the size of the area stimulated
    - Increases the longer the duration of the current flow

ELECTRICAL SAFETY:

- Electrical equipment safety: medical, classification/types of equipment, symbols
- Circuit breakers

General measures

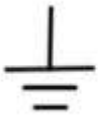
- Regular testing of electrical equipment
- Reporting of faults and regular maintenance
- Ensure patients are not in contact with earthed objects
- Shoes with insulated soles
- Antistatic flooring
- Control of relative humidity
- Non-sparking switches and plugs

Equipment design

- South African Bureau of Standards - SANS 60601-1-11 - General requirements for basic safety and essential performance of medical electrical equipment
- Equipment may be classified based on:
    - *Method of protection*: Class I, II or III
    - *Degree of protection provided:* type B, BF or CF

Class I equipment

- All accessible conductive parts connected to earth wire
    - Ensures accessible parts maintained at zero potential
    - Provides low resistance pathway for aberrant charge to be transmitted safely to earth
- Additional fuses at the equipment end of the power cable in both live and neutral connectors
- If an appliance fault causes a high current to flow down the earth wire, the increased current will melt any protective fuses, breaking the circuit and reducing the risk of electrocution

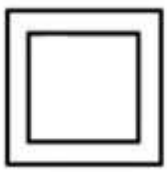


Earth

Protective Earth

Class II equipment

- Double or reinforced insulation
- Minimal chance of a person coming into contact with any faulty live components within the device
- No earth connection



Class III equipmentPowered by internal battery or safety extra low voltage (SELV).

- Specifications for SELV:
    - Voltage must be <25V if AC or <60V if DC
    - No earth connection (usually involve floating circuit)
    - Very low risk of accidental contact with a higher voltage
- Not considered sufficient protection for medical devices

Degree of protection

- Designated by type designation- B, BF, CF
- Quantified by maximum permissible leakage currents, both under normal conditions (NC) and single fault conditions (SFC)

Type B

- May be Class I, II or III
- Least stringent requirements (one level up from normal domestic appliances)
- Used for equipment that does not have any conducting parts in connection with the patient, e.g., a ventilator.

- **Maximum allowable leakage currents:**

Supply/Class	***NC (mA)***	**SFC (mA)**
AC (Class I)	<0.1	<0.5
AC (Class II)	<0.1	<0.1
DC	<0.01	<0.05

Type BF

- As for Type B equipment, with the addition of an isolated or floating circuit to improve safety
- Uses a transformer to create a secondary circuit that is in contact with the patient but has no direct conductive connection to the power supply
- More suitable for direct patient contact
- The floating circuit has no earth (mains circuit is earthed)
- Electrocution can only occur if floating circuit accidentally earthed at same time as an internal electrical fault (device should be fitted with a line isolation monitor to warn if this occurs)
- Examples: ECG monitoring, patient warming devices

- **Maximum allowable leakage currents:**

Supply/Class	***NC (mA)***	**SFC (mA)**
AC (Class I)	<0.1	<0.5
AC (Class II)	<0.1	<0.1
DC	<0.01	<0.05

Type CF

- May be Class I or II
- Most stringent requirements- provides high degree of protection against microshock
- Mains- or battery-powered
- Also uses floating circuit, but has much lower maximum permissible leakage currents
- Examples: PA catheters, internal temporary pacing systems

- **Maximum allowable leakage currents:**

Supply/Class	***NC (mA)***	**SFC (mA)**
ALL	<0.01	<0.05

Defibrillator-safe

- Can be applied to all type classifications, but most commonly type BF and type CF
- Device can be left connected to patient during defibrillation

Symbols on electrical equipment:		
 Double Insulated (Class II)	 Type B	 Type BF
 Type B, defibrillator safe	 Type BF, defibrillator safe	 Type CF
 Type CF, defibrillator safe	 Equipotential earth point	
 Waterproof	 splashproof	 Drip proof

Equipotentiality

- Potential difference between equipment and earth may differ to that of other equipment in close proximity
- If someone touches both pieces of equipment at the same time, electrical current could flow through the user from the equipment at higher potential to the piece at lower potential
- Equipotentiality: terminals of equipment in close proximity are connected → potential differences are brought into equilibrium → ↓ electrocution risk

Circuit breakers

- Earth leakage circuit breakers provide further protection against electrocution
- Electromechanical devices that disconnect equipment power supply in the event of a fault causing current to flow down the earth wire
- Voltage or current operated

Voltage-operated circuit breakers

- Detect rise in potential difference between protected metalwork (e.g., metal casing) that is connected to earth and distant earth reference electrode
- Once potential ≥50V detected → solenoid-driven circuit breaker activated → downstream equipment isolated from mains supply
- Now largely replaced by current-operated earth leakage circuit breakers

Current-operated earth leakage circuit breakers

- Compare the current in live wire to current in neutral wire
- Transformer with equal windings of both live and neutral wires around core, along with third winding that is connected to circuit breaker
- Normally, current in live and neutral wires of equal magnitude, but opposite direction → cause equal but opposite magnetic flux in the transformer core → cancel each other out
- If a fault causes current leakage, not all of the current will return via the neutral wire → difference from that of live wire → residual magnetic flux → current induced in third wire → solenoid-driven circuit breaker activated → power supply disrupted
- Very sensitive: triggered by 30mA passing for just a few milliseconds- greatly reduce the risk of electrocution

DIATHERMY:

- Surgical tool that uses electrical current to cut tissue and coagulate blood
- Utilises the heating effect of high frequency alternating current (0.5-1.0mHz) passing through the high impedance of body tissues
- The amount of heating produced by the current is dependent on the current density (amount of current flowing per unit time) and duration of contact
- Heating is proportional to the square of the current and inversely proportional to the size of the contact area
- Monopolar or bipolar

Monopolar diathermy

- Consists of an active electrode (probe) and a neutral plate (diathermy/ground plate)
- Probe: small contact area + high current density + high resistance = large heating effect
- Ground plate: large contact area + low current density + low resistance = very little heating effect
- Current flows through the probe at a high current density, but returns via the plate at a low current density, due to the large surface area of the plate
- Overall power delivered: 100-200W

Bipolar diathermy

- Bipolar diathermy contains 2 probes in a pair of forceps
- Small electrode surface rea = high current density → heating of tissue held in forceps but little effect on surrounding tissues
- Overall power ≈ 40W

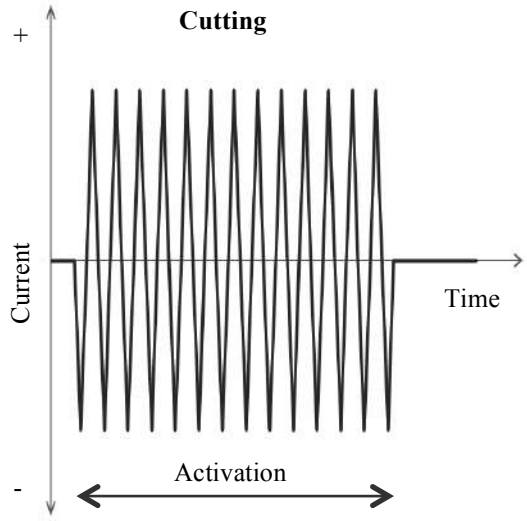
Diathermy effects

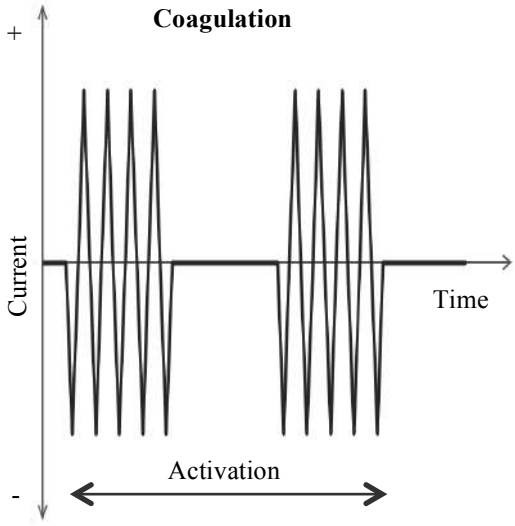
- Microscopically:
    - Higher temperatures and current densities = coagulation, denaturing of proteins
    - Lower temperatures and current densities = dessication, cellular details preserved
- Macroscopically:
    - Widespread tissue destruction
    - Vaporisation- requires high current density and lead to cutting of tissues

Cutting and coagulation

- Cutting:
    - Continuous higher frequency (≈400kHz), lower voltage (400-1kV), higher power (>100W)
    - Sustained high frequency sine wave current
    - Tissue vaporisation
- Coagulation:
    - Interrupted/modulated current- pulsed sine wave
    - Lower frequency (250-400kHz), higher voltage (<9kV), lower power (usually <100W)
    - Interrupted current = tissue cooling so does not vaporise
- Blended:
    - Combination of cutting and coagulation current patterns → mixture of cutting and coagulation effects

Diathermy waveforms





Diathermy hazards

- Burns
- Electrocution
- Pacemaker interference
- Interference with monitoring
- Fires and explosion

Diathermy burns

Cause	***Prevention***
Incorrect ground plate positioning	Careful positioning in suitable location Ensure good contact made
Ignition of flammable skin preps	Allow adequate drying time
Accidental earthing	Ensure no contact with potential earthing objects
Inadvertent probe activation	Store probe in designated holder Audible note when probe activated

Diathermy electrocution

- Cause: equipment fault or inadvertent earthing providing an alternative route
  Prevention:
  - Check ground plate site to ensure good contact
  - Audible alarm if the ground plate is dislodged or not plugged in correctly
  - Isolated/floating patient circuit: protection from electrocution due to internal fault (not earthed)
- Cause: monopolar ground plate earthed- may earth patient if contact with other faulty equipment
  Protection: isolating capacitor in plate's earth line- high impedance to potentially harmful frequencies but allows high frequency diathermy current conduction

Diathermy-induced pacemaker interference

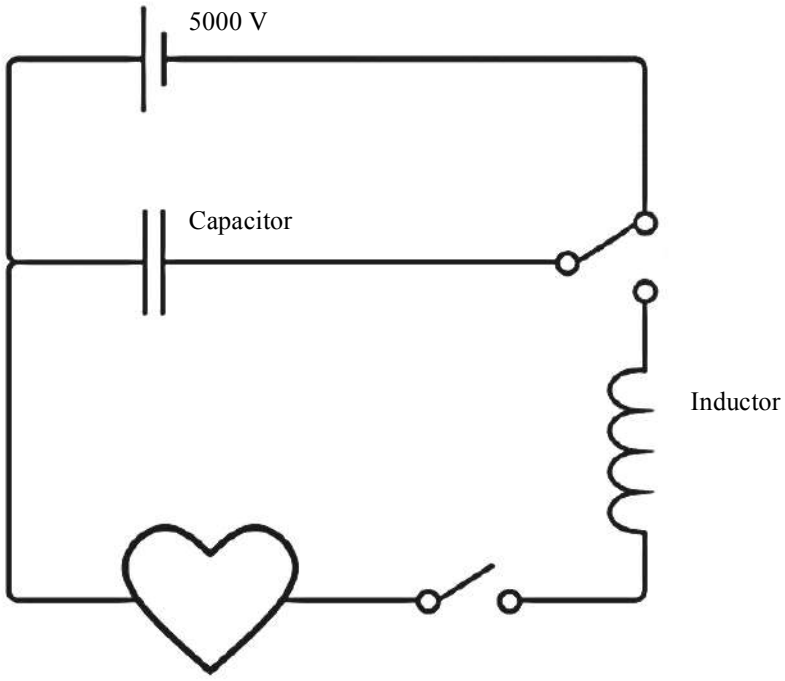
- Ideally avoid diathermy if pacemaker/ICD
  - Electrical interference may cause device damage/reprogramming or incorrect ICD activation
- Bipolar safer than monopolar
- If monopolar necessary:
  - Short bursts
  - Ground plate secure at distant site

- If very pacemaker dependent → asynchronous mode
- Temporarily deactivate ICD
- Temporary pacing and emergency trolley available
- Some pacemakers now protected against diathermy

Diathermy-induced monitoring interference

- Typically affects ECG and transoesophageal echocardiography
- May be reduced by electrical filters
- Potential risk of treating artefact

DEFIBRILLATION:



- A defibrillator is a device used to restore normal cardiac rhythm by delivering electrical energy across the heart, causing coordinate mechanical depolarisation
- Synchronised cardiac contraction →refractory period →sinus rhythm
- DC shock: less myocardial damage and arrhythmia tendency than AC
- 5000V: achieved by using a step-up transformer and then converted to DC using a diode/rectifier

Defibrillator circuit

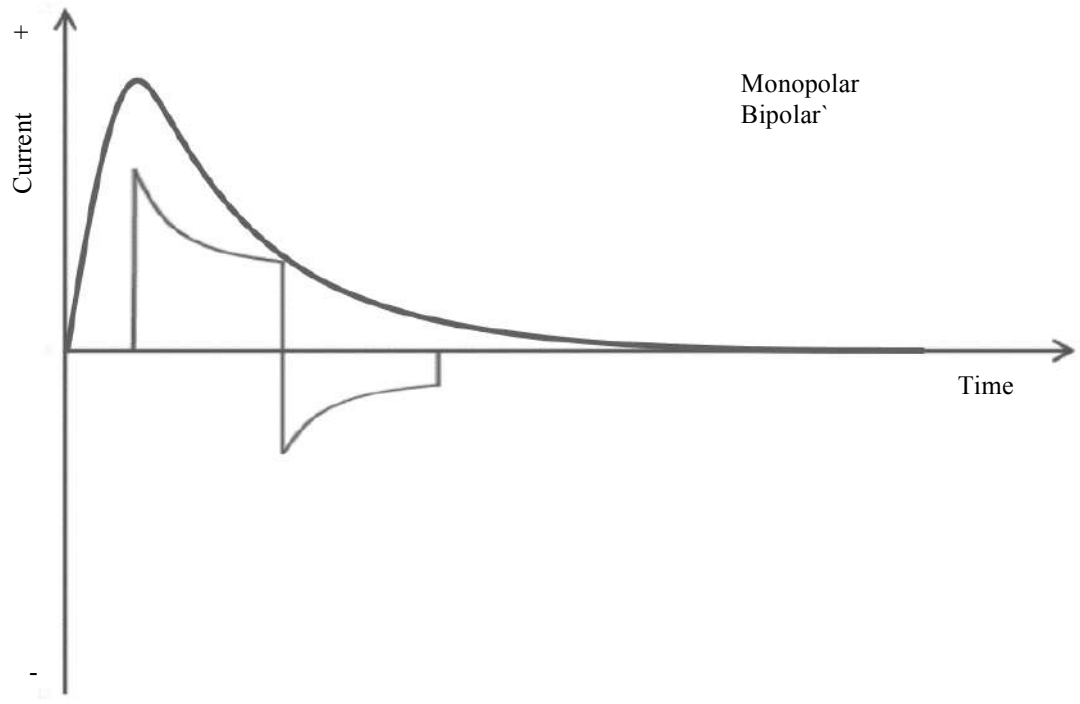
- *Capacitor*
  - Used to store charge
  - Potential difference between plates = 5000-8000V
  - During defibrillation, the stored energy which is released is proportional to the potential difference ($E= ½ CV^2$)
- *Inductor*
  - Used to smooth and prolong discharge duration
  - Coil of wire wrapped around ferrous core known as a former
  - Current induces opposing magnetic flux → smooths and controls current shape
- During charging, the upper switch is in the position, as shown, and electricity flows through only the upper circuit, charging the capacitor.
- During discharge, the top switch moves to the downward position and the lower switch closes, so that the charge previously stored on the capacitor can be delivered to the patient.
- Delivery is via two electrodes which may take the form of external sticky pads, internal paddles or wires to an implanted device

Energy delivery

- Defibrillation: DC pulse of <30A for 3msecs with 5000V produced
- Energy delivered to patient is always less than charged stored by the capacitor as some energy is lost within the inductor and patient provides some impedance to current flow
- Thoracic impedance is ≈ 50-150Ω but ↓after first shock
- The shock delivered may have either a monophasic or biphasic waveform

Monophasic vs Biphasic

- *Monophasic waveform*
  - Dampened sinusoidal wave (Lown-type waveform)
  - Current flows in one direction only between the two electrodes
- *Biphasic waveform*
  - ↓ myocardial damage, more effective at terminating VF
  - Current flows in both directions in rapid succession (1 cycle ≈10 msecs)
  - Waveform current strength and duration may vary, depending on settings
  - More sophisticated devices are able to measure and correct for transthoracic impedance
- Monophasic defibrillators use 360J of energy and biphasic use 150J. Internal defibrillators use 20-50J. Energy delivered to children is weight-specific at 4J/kg.
- *Defibrillator waveforms:*



Synchronised cardioversion

- Defibrillator can also be used to electrically cardiovert arrhythmias e.g., rapid AF and SVT
- Lower energy used, ≈20-200J
- Current delivery must be synchronised with patient's cardiac rhythm to prevent delivery of shock during early ventricular repolarisation as may trigger ventricular fibrillation – 'R on T phenomenon'
- This is achieved by the use of additional ECG leads which connect patient to defibrillator.

Defibrillator hazards

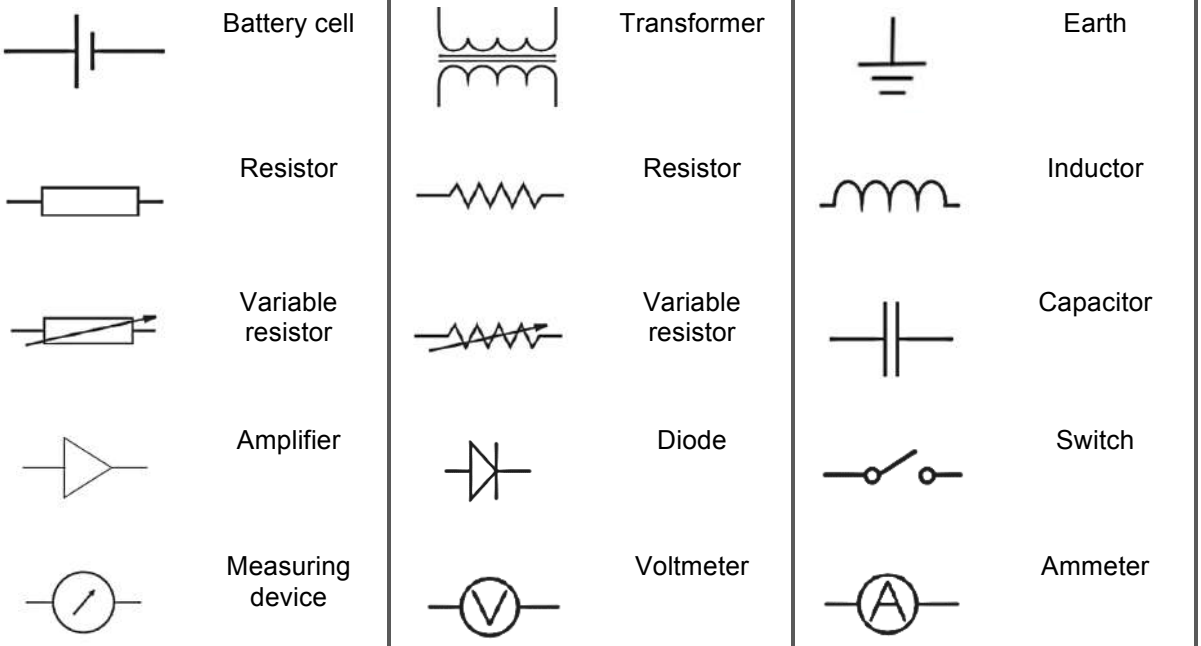
- Electrocution:
  - Remove others from patient vicinity during shock delivery
  - Only charge once the pads are on the patient
  - Dump charge if not required before removing pads from patient

- Electrical burns:
  - Ensure patient not wet, as water reduces impedance
  - Remove any earthing objects, e.g. drip stands
  - Place pads away from any metal, e.g. skin clips, implanted devices, jewellery
- Fire/explosion:
  - Unless in closed system, move O_2 > 1m away during shock delivery
  - Remove potentially flammable transdermal patches, e.g. GTN
- Remove any equipment that is not defibrillator safe

SUMMARY OF TOPICS COVERED:

- Concepts: charge, conductance, AC and DC, series and parallel circuits, electromagnetism, and induction
- Definitions; current, voltage, resistance, reactance, impedance, capacitance, and inductance
- Units of measurement: coulomb, ampere, volt, ohm, henry
- Components; batteries, resistors, capacitors, inductors, transformers, transistors, diodes, and amplifiers
- Principles of a Wheatstone bridge and electrical filters
- Electrical symbols: cell, battery, resistor (2), variable resistor (2), transistor (2), capacitor, bulb, switch, diode (2), LED, inductor, transformer, amplifier

Electrical Components:



- Mains electricity: AC @ 50 Hz RMS voltage =230 V
- Domestic supply: Live, neutral and earth wires, fuses ↑ safety
- Hazards of electricity: electrocution, burns, interference with monitoring, fire
- Effects of electrocution depend on: current magnitude, type, pathway, density and duration.
- Macroshock= electrocution through intact skin, microshock = in close vicinity to the heart
- ↓ electrocution by: general measures, equipment design, equipotentiality, floating circuits, circuit breakers
- Equipment methods of protection: class I (earthed), class II (double insulated), class III (battery/SELV)
- Degrees of protection: type B (least stringent), type BF (floating circuit, patient connection OK), type CF (most stringent, cardiac connection OK)
- Diathermy uses high frequency (0.5-1MHz) to cut and coagulate tissues.
  - Monopolar or bipolar

  - Cutting = continuous high-frequency sine wave current, coagulation = pulsed sine wave of lower frequency but higher voltage
  - Hazards; burns, electrocution, interference with cardiac devices and monitoring, fire.
- Defibrillators use DC pulse of up to 30amps for 3ms at 5000V.
  - Contain capacitor to store charge and inductor to modulate current flow.
  - Monophasic defibrillation = 360J in one direction
  - Biphasic defibrillation = 150J rapidly in two alternate directions
  - Hazards: electrocution, burns, and fire

FURTHER READING:

- Singh SK, Ingham R, Golding JP. **Basics of electricity for anaesthetists.** *Continuing Education in Anaesthesia Critical Care & Pain*, 2011; 11:6, 224–228.
- Boumphrey S, Langton JA. **Electrical safety in the operating theatre.** *BJA CEPD Reviews,* 2003.; 3:1, 10-14.

PAST CMSA FCA(I) SAQ's:

2017

Diathermy
a) What is the difference between monopolar and bipolar electrocautery, and why is this important? (3)
b) Briefly explain why, with respect to size, the bigger a diathermy return pad is, the better? (1)
c) What current strength is typically delivered by electrocautery? (1)
d) What Voltage is typically achieved by a diathermy machine? (1)
e) Why does using diathermy not commonly result in ventricular tachycardia and or fibrillation? (1)
f) List 3 mechanisms by which electrocautery can result in unintentional burns. (3)

Capacitors
a) What is a capacitor? (1)
b) What are the components of a capacitor? (2)
c) Give an example of a capacitor used in medical practice. (1)
d) What is the SI unit for measuring capacitance? (1)
e) What factors determine the capacitance of a capacitor? (3)
f) Which device is put in the output limb of a capacitor to lengthen current delivery? (1)
g) Draw the symbol of a capacitor as depicted in an electrical circuit diagram. (1)

Flow measurement
c) List 2 safety mechanisms to prevent build-up of electrostatic charge in a flow meter tube. (2)

2018

Question 3
a) Define the following units and explain what they measure
  i) Ampere. (2)
  ii) Volt. (2)
  iii) Ohm. (2)
b) Define Ohm's law by means of an equation. (1)
c) Relate blood pressure and cardiac output to Ohm's law by means of an equation. (1)
d) Describe the main function of each of the following electrical components
  i) Capacitor. (1)
  ii) Inductor. (1)

Question 9
a) Draw and label a schematic diagram showing the major components of a monopolar diathermy circuit. (6)
b) Surgical burns can occur at remote sites not involved in the surgery when monopolar diathermy is used. Provide 4 examples of how this may occur, providing a brief explanation in each case. (4)

Question 15
a) In pacemakers, what does the coding VVI stand for? (3)

b) Draw a schematic circuit of a unipolar pacemaker. (5)
c) What is the major disadvantage of unipolar pacemakers? (1)
d) How much current needs to be induced in the myocardial lead of a unipolar pacemaker for microshock to occur? (1)

2019

Question 12
a) What is a pressure transducer? (1)
b) What is a strain gauge, and how does it work? (2)
c) Describe how an unknown resistance can be measured by means of a Wheatstone bridge. (5)
d) Why must a pressure transducer be zeroed and levelled? (2)

Question 13
a) Describe the classification (Class 1-3) of electromedical equipment according to protection it provides against electric shock. (9)
b) Explain how a space blanket can potentially become an electrical hazard when used in theatre. (1)

Question 18
a) What is the function of the capacitor in a defibrillator circuit? (2)
b) What is the symbol for a capacitor in an electrical circuit diagram? (1)
c) Explain the function of an inductor in a defibrillator circuit. (1)
d) What is the advantage of biphasic waveforms in a defibrillator? (3)
e) Describe three ways to reduce the risk of defibrillation burns. (3)

Question 12
a) List 5 pacemaker complications that may be caused by MRI scanning. (5)
b) List the 5 components of the pacemaker pulse generator (5)

Question 14
a) Define Capacitance. (2)
b) Provide the formula for the following
i) Coulomb. (2)
ii) Farad. (2)
c) Draw & label the components of a monophasic defibrillator circuit when it is charging. (4)

2020

Question 12
a) Define capacitance and give its unit of measurement. (2)
b) What factors determine capacitance? (2)
c) Tabulate three differences between a monophasic and biphasic defibrillator. (6)

Notes

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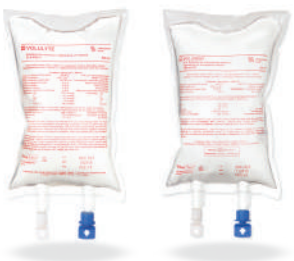

When minutes and hours matter

INDICATIONS: **Volulyte/Voluven,** in conjunction with crystalloids, is indicated for the treatment of adult and paediatric patients, excluding neonates, with acute hypovolaemia associated with trauma and/or surgery, to restore haemodynamic stability.

The underlying cause of the hypovolaemia should be corrected and the patient should be continuously monitored.[1]

Reference: 1) SA Professional Information, Volulyte/Voluven.

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< BACK TO INDEX

Renal Autoregulation

Prof. Busisiwe Mrara

HOD, Dept of Anaesthesia & Critical Care
Walter Sisulu University

At the end of this lecture; attendees should be able to:

- Understand renal autoregulation
- Explain various physiological mechanisms of renal autoregulation
- Describe modulation of renal autoregulation
- Discuss perioperative implications of renal autoregulation
- Apply the theoretical concept to real-life case management

Introduction

"***What engineer, wishing to regulate the composition of the internal environment of the body on which the function of every bone, gland, muscle, and nerve depends, would devise a scheme that operated by throwing the whole thing out 16 times a day and rely on grabbing from it, as it fell to earth, only those precious elements which he wanted to keep?" Homer Smith (1895-1962)***

As applicable now as 400 years ago, this statement reflects the renal system's complexity and novelty. It is a marvel to consider how the adaptation of purifying the blood by throwing everything away and then reclaiming only selected substances such as glucose, amino acids, fluids and electrolytes, is probably a more energy- and resource-economic physiological processes than the reverse sequence. Basic science research continues to improve our understanding of this essential organ. Much still needs to be done to understand renal physiology and pathophysiology better to facilitate the development of preventative and curative renal disease interventions.

A good understanding of renal physiology and its monitoring is essential for the Anaesthetist, whose role is to maintain the internal milieu by balancing intraoperative fluid/blood loss with intake and managing acid-base derangements.
Renal physiology and pathophysiology concepts continue to evolve with improved understanding with the advent of novel imaging tools, tissue staining techniques, genomic and metabolomic studies.
The scope of renal physiology is enormous and cannot be covered in one lecture. This lecture aims to provide an update on some aspects of renal autoregulation.

What is renal autoregulation?

Renal autoregulation, the maintenance of renal blood flow and glomerular filtration over a defined range of renal perfusion pressures, is an adaptation described in almost all organs. It has been known from as far back as 1902 when W.M Bayliss described the local arterial wall reactions to changes in intraluminal pressure in dogs. He observed that *"The peripheral powers of reaction possessed by the arteries is of such a nature as to provide as far as possible for the maintenance of a constant flow of blood through the tissues supplied by them, whatever may be the height of the general blood-pressure…" (1)*
In the kidney, impaired autoregulation is recognized as a critical pathway to acute kidney injury (AKI) and chronic kidney injury (CKD) from pathologies such as shock, sepsis, diabetes and hypertension. The Anaesthetist is responsible for intraoperative haemodynamic management and organ protection and should thus have a good grasp of renal autoregulation.

The process serves four essential functions in the kidney:

1. Providing a basal vasomotor tone regulating renal vascular resistance.
2. Buffering the transmission of the varying renal perfusion pressures to protect the glomerular capillaries and parenchyma from excessive pressure and barotrauma.
3. Preventing excessive loss of plasma by adjusting glomerular filtration rate (GFR) to tubular filtrate flow.

4. Preserving glomerular filtration and medullary perfusion in states of reduced renal perfusion pressure to ensure ongoing clearance of metabolic wastes and recovery of filtered electrolytes and nutrients. (2)

The process is described to have an intrinsic component solely regulated within the kidney and an extrinsic component regulated by circulating hormones and extrinsic nerves.
Renal autoregulation is mediated by renal vascular resistance changes in the medium-sized pre-glomerular arteries of the renal cortex, mainly the afferent arterioles. It maintains renal blood flow (RBF) constant between mean arterial pressures (MAP) of about 70 to 130 mmHg under normal physiological states.
The efferent arterioles contribute to the process to a lesser extent. They have been described to be activated only in conditions of low renal perfusion pressure and activation of the renin-angiotensin system (RAAS).

What are the physiological mechanisms of renal autoregulation?

Two mechanisms are described to mediate intrinsic renal autoregulation: the myogenic response and tubuloglomerular feedback.

1. Myogenic response

The myogenic response (MR) is characterized by a decrease in vessel diameter after an increase in transmural pressure and the opposite effect after a reduction in this pressure. This is effected by the activation of vasoconstriction of the pre-glomerular arterioles, particularly the afferent arterioles.

The response is rapid and almost immediate, with a response time of 3-10 seconds after the pressure change, compared to > 20 seconds for the slower tubuloglomerular feedback. Studies of the frequency response of autoregulation show that the oscillating pressure of normal physiology causes sustained contractions, and that the myogenic response is targeted at the systolic pressure and not the mean pressure. The response is neither influenced by endothelial function nor by neural signals.

The details of the physiological process are illustrated in detail in figure 1. The response is described to occur in three stages: membrane sensation for mechanical stretch, transduction of the stretch into a cytosolic signal, and then the contractile response to the signal.

The putative mechanisms of the mechano-transduction include:

1. Interaction of cell surface integrins with extracellular matrix proteins such as fibronectin.
2. Epithelial sodium channel (ENaC) opening.
3. Non-selective cation channel activation: transient receptor potential melastatin 4(TRPM4) and transient receptor potential canonical 6 (TRPC6) which promote Na^+ and Ca^{2+} entry through Gq-protein linked second messenger systems, leading to activation of phospholipase C (PLC) and production of diacylglycerol (DAG) and inositol triphosphate(IP3).

These events lead to the influx of Ca^{2+} into the vascular smooth muscle cell (VSMC) through the L-type voltage-gated calcium channels (VGCC). The calcium stimulates substantial calcium release from the sarcoplasmic reticulum, which binds to calmodulin. The calcium-calmodulin complex activates myosin light chain kinase(MLCK), which phosphorylates myosin light chain to prepare for actin-myosin interaction and contraction.
Also, protein kinase C (PKC), activated by DAG, propagates the response by stimulating the VGCC further and blocking significant conductance potassium (BK) channels. BK channels are also blocked by 20-Hydroxyeicosatetraenoic acid (20-HETE), a metabolite of arachidonic acid, resulting in the prolonged opening of the VGCC. Inhibitors of the synthesis of 20-HETE, such as nonsteroidal anti-inflammatory drugs, have been found to impair renal autoregulation. (3)

The process culminates in calcium-mediated vasoconstriction of the VSMC and afferent arteriolar constriction.

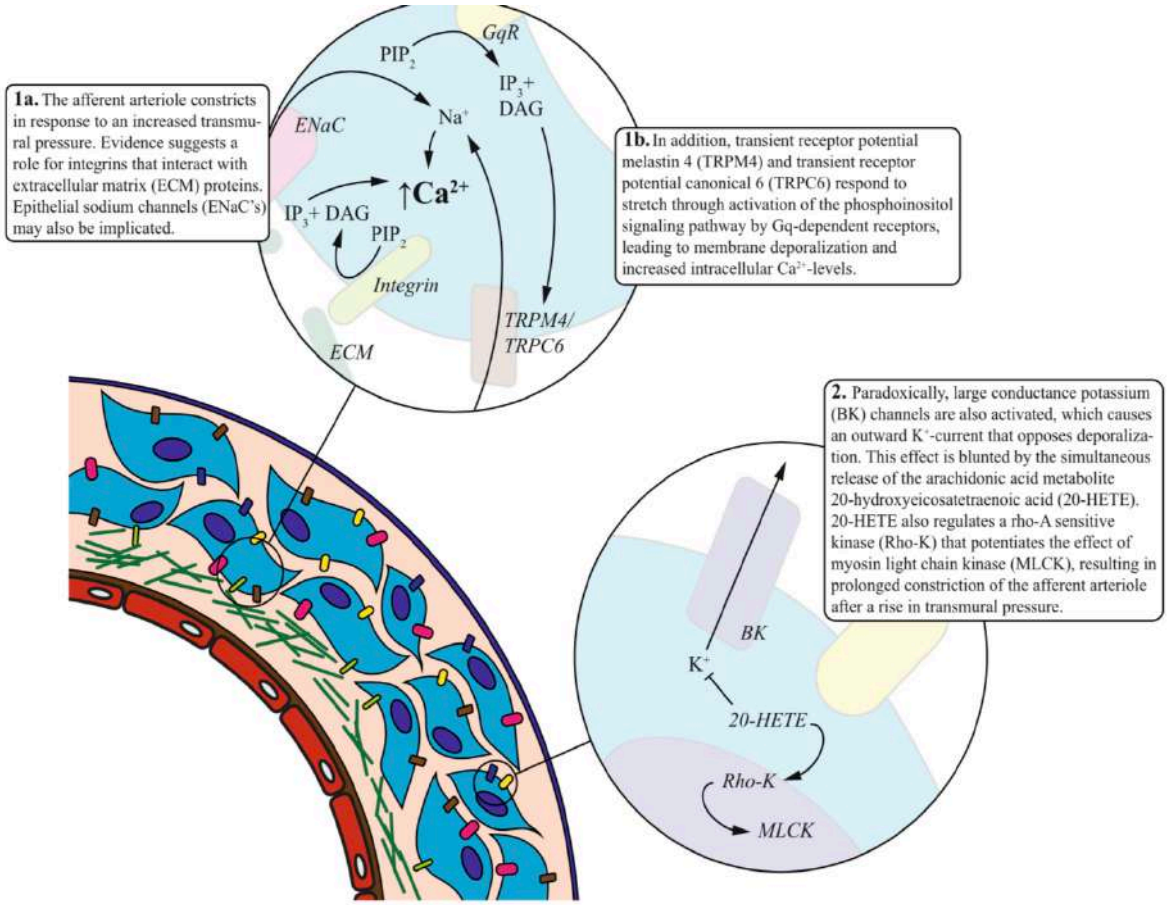

Figure 1: Schematic flow diagram of the myogenic response Adapted: Post and Vincent, Critical Care (2018) 22:81 https://doi.org/10.1186/s13054-018-1962-8

2. Tubuloglomerular feedback

Tubuloglomerular feedback (TGF) executes renal autoregulation by creating a negative feedback loop that senses sodium chloride in the tubular fluid reaching the macula densa in the distal nephron through signaling mechanisms, causing afferent arteriolar vasoconstriction. This maintains GFR and tubular filtrate flow at a constant rate by reducing GFR to match the amount of processed tubular fluid.

The afferent arteriole's relationship with the early segment of the distal tubule, the juxtaglomerular apparatus (JGA), is shown in figure 2 and is the adaptation enabling TGF.

The JGA comprises:

1. Afferent and efferent arterioles,
2. Macula densa, a specialized group of distal tubular cells that secrete renin.
3. Lacis cells (Goormaghtigh cells, extraglomerular mesangial cells). Lacis cells form a pyramid situated between the afferent and efferent arterioles, and with its base on the macula densa and apex continuous with the glomerular mesangium.

The JGA is critical in tubuloglomerular feedback control of renal blood flow, glomerular filtration rate, and tubular control of renin secretion. The afferent arteriole contacts the renal tubules in the macula densa (MD), located in the transition region between the ascending section of the loop of Henle and the distal convoluted tubule. Fig. 2 also shows the second point of contact of the AA with the connecting tubule (CNT) region, closer to the distal convoluted tubule. The arrangement of two communication points, including the CNT region, is described mainly with superficial nephrons, and less with deeply embedded nephrons. The CNT connection's clinical significance is in the modulation of the primary tubuloglomerular feedback mechanism and is described in some detail later.

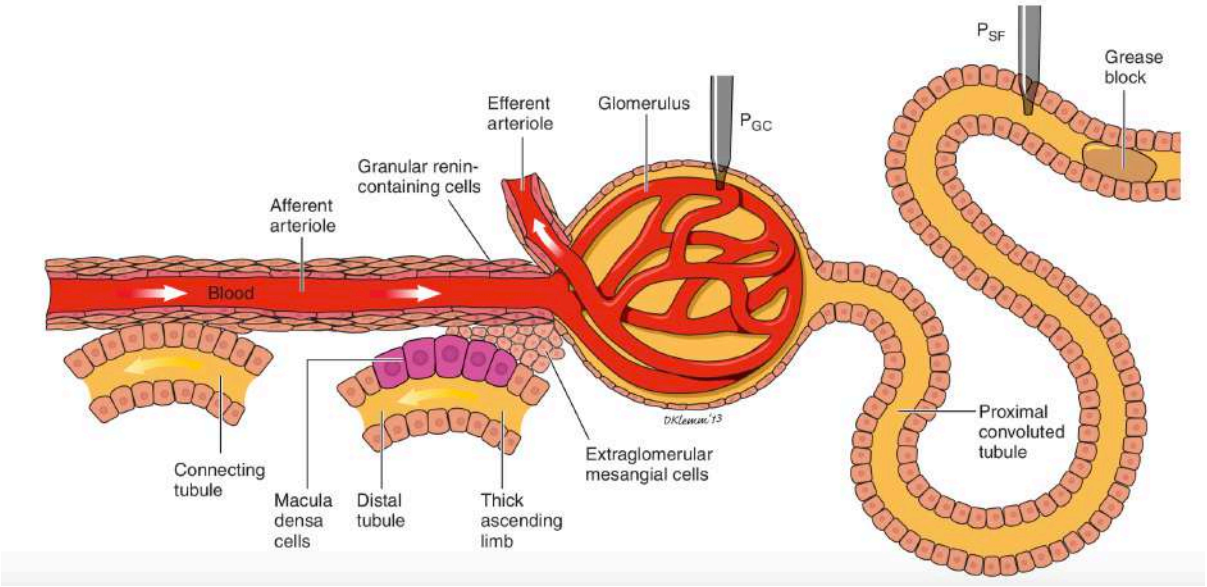

Figure 2: Schematic diagram of the juxtaglomerular apparatus showing contact of the tubules with the afferent arteriole. The tubules contact the afferent arteriole at two areas, the thick ascending limb of the loop of Henle and the connecting tubule. The two points of contact modulate tubuloglomerular feedback. Adapted: Carlström M, **Wilcox CS**, Arendshorst WJ.Physiol Rev. 2015 Apr;95(2):405-511. doi: 10.1152/physrev.00042.2012 (4)

The TGF process is described in detail in figure 3. Increased renal perfusion pressure (RPP) causes increased filtration of NaCl. Thus, a large load of filtered sodium is delivered to the macula densa in the thick ascending limb (TAL) of the loop of Henle. At the TAL, the sodium-potassium two chloride (NKCC2) exchanger reabsorbs the NaCl, thus activating intracellular Na and sodium-potassium ATPases, raising intracellular Ca^{2+}. These events trigger ATP breakdown to adenosine which acts on Adenosine 1A receptors in the afferent arteriole to cause vasoconstriction. The processes leading to vasoconstriction are similar to the myogenic response in activating PLC, activating DAG and IP3 and finally PKC and MLCK. The process is also potentiated by the opening of VGCC and blockade of BK channels by 20-HETE. Also, TGF is modulated by angiotensin II through purinergic receptors. (3)

Given the convergence of the pathways leading to afferent arteriolar vasoconstriction, the myogenic response and tubuloglomerular feedback are synergistic in achieving afferent arteriolar vasoconstriction, the path to reducing glomerular blood flow and GFR.

The autoregulatory mechanisms are described to have the most significant impact on the afferent arteriole and to have a modest vasodilatory effect on the efferent arterioles. Efferent arterioles in a preconstricted state have been shown to dilate in response to increased macula densa NaCl, in a process mediated by activation of adenosine A_2 receptors. Thus, TGF changes efferent arteriole resistance in the opposite direction as compared to the afferent arteriole, possibly amplifying TGF regulation of intraglomerular capillary hydrostatic pressure and GFR. (3)

Chloride Role in Tubuloglomerular Feedback

The role played by chloride handling in renal autoregulation has recently been explored(5). In the setting of reduced renal perfusion pressure, reduced macula densa chloride concentration stimulates the release of renin and local prostaglandins, thus maintaining GFR by afferent vasodilatation and efferent vasoconstriction. Excess chloride from normal saline and/or hyperchloremia increases distal chloride delivery to the macula densa, resulting in a reduced GFR from afferent vasoconstriction, mediated by thromboxane and adenosine. Efferent arteriolar vasodilatation also occurs from reduced renin and angiotensin II levels. In the macula densa, the influx of chloride via NKCC2 increases intracellular chloride and subsequent basolateral chloride exit with ATP breakdown.
In juxtaglomerular (JG) cells of the afferent arteriole, angiotensin II increases intracellular calcium, which triggers chloride efflux through calcium-activated chloride channels, leading to cell depolarization and VSMC contraction.

Calcium-activated chloride channels are also present in mesangial cells; chloride efflux-mediated cell depolarization triggers more calcium influx through voltage-dependent calcium channels, leading to sustained VSMC contraction, and renal ischaemia.
This is the putative pathway to the causation of AKI by fluids containing super-physiological amounts of chloride.

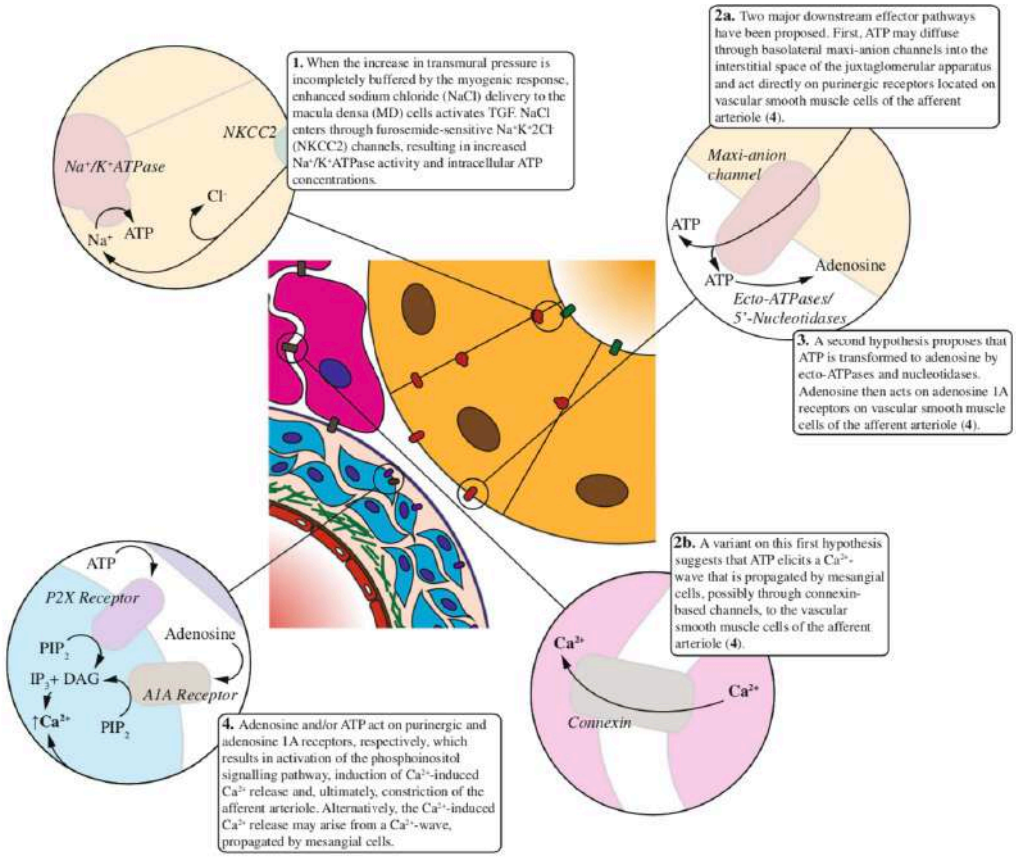

Figure 3: schematic representation tubuloglomerular feedback. Adapted from Post and Vincent, Critical Care (2018) 22:81 https://doi.org/10.1186/s13054-018-1962-8

Modulation of Renal Autoregulation

As for most physiological processes, modulatory systems for autoregulation are in place. One is the release of vasodilatory mediators, which is stimulated after a period of vasoconstriction. The process is initiated by shear stress from vasoconstriction, which stimulates the release of nitric oxide, prostaglandin E2, prostacyclin and epoxyeicosatrienoic acids from the endothelium leading to a vasodilatory effect.
A novel mechanism to modulate TGF has been described, related to the connecting tubule (CT) contact with the afferent arteriole, shown in figure 2. The increased filtrate and NaCl flow through the CT stimulate the production of mediators of afferent arteriolar vasodilation. This mechanism is thought to blunt TGF sensitivity, in the long run, to allow the kidney to increase NaCl excretion in the face of increased sodium intake (6).

Renal autoregulation also works closely with the renin-angiotensin-aldosterone system (RAAS). Briefly, the RAAS is activated by low renal blood flow states and low sodium levels. Afferent arteriole JG cells convert the precursor prorenin (circulating in the blood) into renin. Plasma renin then converts angiotensinogen, released by the liver, to angiotensin I. Angiotensin I is subsequently converted to angiotensin II (ATII) by angiotensin-converting enzyme (ACE) found on the surface of vascular endothelial cells, predominantly in the lungs. Angiotensin II is a potent vasoconstrictive peptide, which increases systemic blood pressure. Angiotensin II also stimulates the secretion of aldosterone from the adrenal cortex, which increases the reabsorption of sodium in the distal tubule, enhancing the reabsorption of water into the blood and causing the excretion of potassium (to maintain electrolyte balance). This increases the volume of extracellular fluid in the body, which also increases systemic blood pressure and maintains RPP and RBF. (7)

ATII effects in the kidney include vasoconstriction of the interlobular artery and afferent and efferent arterioles (most significant effect on the latter). ATII also enhances afferent arteriolar response to TGF, and constriction of the glomerular mesangium.

Renal Autoregulation: Perioperative Implications

1. Clinical evaluation

Renal autoregulatory assessment is currently technically challenging and may improve with further research and refinement of assessment tools.
Renal doppler derived indices are increasingly used to assess renal blood flow and vascular resistance and have been used to predict AKI in septic and haemorrhagic shock(2). The technique has limited value in evaluating rapidly changing renal haemodynamics and is hindered by the difficulty in obtaining a steady acoustic window due to the displacement of the kidney during rapid respiration.
Contrast ultrasound and phase-contrast magnetic resonance imaging are gaining traction for renal blood flow measurement, though limited by measurement ability over only a short time.
Near-infrared spectroscopy (NIRS) allows continuous assessment of renal blood flow and has been used in paediatrics. The range of penetration depth of the beam in the current technology is inadequate for use in adults. (8)

2. Clinical Application

Patients with severe chronic hypertension have been found to have a rightward shift of the autoregulatory curve, an adaptive response to reducing chronic kidney disease risk. Generalized atherosclerosis and type 2 diabetes mellitus are associated with impaired autoregulation.

Septic, ischaemic and haemorrhagic shock are associated with a reduction in autoregulatory efficiency after a variable period of shock, 12 to 18 hours.
Vasopressor use, particularly noradrenalin, has been found to cause a rightward shift of the autoregulatory curve and reduce the response's efficiency, while haemodilution could also impair autoregulation. (8)

In all these conditions, perioperative blood pressure management should ideally be precise to maintain renal perfusion and protect the kidney.

Conclusion

Renal autoregulation is an essential physiological adaptation to changing renal blood flow, aimed at maintaining renal function while protecting the kidney. The two main autoregulatory mechanisms: the myogenic response and tubuloglomerular feedback, have been presented in detail, with recently explored updates on modulatory mechanisms and the role of hyperchloraemia in tubologlomerular feedback.

Clinical implications of blood pressure management and renal protection in the setting of impaired autoregulation have been discussed.

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MCQ examples

1. Glomerular filtration rate would be increased by:

a. constriction of the afferent arteriole
b. a decrease in afferent arteriolar pressure
c. compression of the renal capsule
d. a decrease in the concentration of plasma protein

2. The renal autoregulatory system involves all the following except

a. Blood flow-metabolic coupling
b. Renin angiotensin aldosterone system
c. Myogenic response
d. Connecting tubule tubuloglomerular response

3. An 80 year old hypertensive female with bowel obstruction is booked for emergency laparotomy. She is taking ibuprofen, losartan, verapamil and amlodipine. Which of the drugs she is taking is least likely to affect renal the renal autoregulatory response to blood pressure changes

a. Ibuprofen
b. Losartan
c. Verapamil
d. Amlodipine

Answers

1. d
2. a
3. d

Notes

The Big Five
Important physics and physiology equations

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Immune Response to Infection

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Notes

Allergy and Hypersensitivity

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Definitions

Hypersensitivity: When a particular condition causes the immune system to overreact, it is referred to as a hypersensitivity reaction. An allergic reaction is one type of hypersensitivity reaction. (*AAAAI American Academy of Allergy Asthma and Immunology*)

Allergy: A chronic condition involving an abnormal reaction to an ordinary harmless substance called an allergen (*AAAAI American Academy of Allergy Asthma and Immunology*)

Atopy: Atopy is a personal and/or familial tendency, usually in childhood or adolescence, to become sensitised and produce IgE antibodies in response to ordinary exposure to allergens, usually proteins. As a consequence, such individuals may develop the typical symptoms of asthma, rhino-conjunctivitis or eczema (*https://allsa.org/wp-content/uploads/2018/03/Guideline-diagnostic-testing-in-allergy.pdf*)

Anaphylaxis: A severe, life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with potentially life-threatening airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes (*WHO International Classification of Disease-11th edition 2019*)

Adverse drug reaction: A general term referring to any untoward reaction to a medication. These are broadly divided into:

- Type A reactions (85-90%%): Predictable reactions that may affect any individual given sufficient dose and exposure and are predictable from the known pharmacology of a drug (i.e. Histamine release from morphine)
- Type B reactions (10-15%): Hypersensitivity reactions. These occur in a susceptible group of patients and have signs and symptoms that are different from the pharmacological actions of the drug.
    - Mostly mediated by immunological mechanisms/inflammatory cells.
    - Sometimes idiosyncratic/exaggerated sensitivity reactions that do not involve the immune system or inflammatory cells

Classification of Anaphylactic reactions by Mechanism

1. Immunological mechanisms (IgE dependent) requires prior exposure to allergen i.e. reactions to Penicillin or NMBA's
2. Immunological mechanisms (IgE independent). Mediated by IgG or IgM, antigen : antibody complexes, and/ or complement) i.e. reactions to Dextran, Protamine
3. Non-immunological mechanisms (Direct mast cell activation) i.e. Reactions to radio-contrast agents, opioids.
4. Idiopathic anaphylaxis (no apparent trigger)

Gell and Coombs Classification of Hypersensitivity

	Type I	Type II	Type III	Type IV
Synonym	Immediate or anaphylactic	Cytotoxic	Immune Complex	Cellular or delayed
Allergens	Pollen, Food allergens, drugs	Drugs, infectious agents, autoimmune reactions	Inhaled molds, Infused foreign proteins (serum sickness)	Contact allergens: nickel in jewelry, fragrances, preservatives.
Latency	Seconds to minutes	Several minutes to hours	3-12 hrs	12hrs to 2 days
Immune reactant	IgE	IgG/IgM	IgG/IgM	T cells
Mechanism	Previous exposure to antigen produces antibodies. Repeat exposure: antigen cross-link antibodies on mast cells or basophils, causes release of immune mediators.	Antigen binds to the host cell membrane. Antibody binds to the antigen on the host cell. Immune system considers host cell as foreign leading to cellular destruction via complement.	Antigen and Antibody binds, forming a circulating immune complex (precipitant). Reticuloendothelial system removes the precipitant.	No antibody involvement. T-cells are activated by an antigen presenting cell. When the antigen is presented again in future the memory T-cells activate macrophages and cause inflammatory response.
Examples	Allergy to Penicillin	Blood transfusion reactions,	SLE, Rheumatoid arthritis, Polyarteritis Nodosa.	Chronic rejection in organ transplants, TB mantoux test.

Cellular mechanisms of hypersensitivity reactions

IgE-mediated immunological mechanisms

Initial sensitisation phase: An allergen/antigen (Ag) gets presented to Mature B cells, which produce specific IgE antibodies to that allergen. IgE antibodies bind to mast cells and basophil receptors. This initial phase of sensitisation is clinically silent. On re-exposure, antigen (Ag) crosslinking of Ag-specific IgE that has bound to the high affinity IgE receptor (FcεRI) on mast cells and basophils occurs. Crosslinking of IgE and its receptor induces a signalling cascade that results in mast cell degranulation. This releases various mediators, preformed (i.e. histamine and tryptase) as well as newly formed (i.e. prostaglandin D2, leukotrienes, Platelet activating factor, thromboxane A2) resulting in clinical manifestations of IgE-mediated anaphylaxis.

IgE-independent immunological mechanisms

These are clinically indistinguishable from IgE-mediated reactions. These include IgG-dependent anaphylaxis, which involves the triggering of mediator release by IgG/ antigen complex crosslinking of FcγRs on macrophages, basophils, and neutrophil as well as anaphylaxis mediated by binding of the complement-derived peptides C3a and C5a to their receptors on mast cells, basophils, and other myeloid cells.

Non-immunological mechanisms

Mast cell activation can occur via non-allergic mechanisms i.e.

- Direct non-specific activation by histamine-releasing agents
- Calcium and phospholipase (C and A2)-dependent mechanisms (i.e. vancomycin and red man syndrome)
- MRGPRX2 (Mast-related G protein-coupled receptor X2) activation, suspected to be involved in non-allergic reactions by NMBAs
- Mastocytosis

Factors that may modulate the onset of allergic and non-allergic anaphylaxis

Stress, infection, dose of allergen, rate of drug injection, chemical property and molecular weight of drug and other host factors will influence the onset of the reaction.

Diagnosing Anaphylaxis (amended criteria for the diagnosis of Anaphylaxis, as proposed by World Allergy Organization anaphylaxis guidance 2020)

1. Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING:

a. Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)
c. Severe gastrointestinal symptoms (e.g. severe cramping abdominal pain, repetitive vomiting), especially after exposure to non-food allergens

2. Acute onset of hypotension or bronchospasm, or laryngeal involvement after exposure to a known or highly probable allergen for that patient (minutes to several hours), even in the absence of typical skin involvement.

Grading Severity of Anaphylaxis

The most commonly used grading system is the **Ring and Messmer** four step grading scale. This starts at Grade 1 with only cutaneous signs and progresses to Grade 4 being cardiac arrest.

A revision has been proposed by the **World Allergy Organisation in 2020**. It looks at the involvement of organ systems to grade the severity, the organ systems being cutaneous, respiratory, conjunctival, gastrointestinal and cardiovascular. Grade 1 and 2 have mild symptoms and are then graded as “Not anaphylaxis”. Grade 3 has lower airway involvement (mild bronchospasm, cough or wheeze) and/ or abdominal cramps which responds to treatment. Grade 4 involves the lower airway (severe bronchospasm) and/ or laryngeal oedema.

Grade 1 (Not anaphylaxis)	Grade 2 (Not anaphylaxis)	Grade 3 (Anaphylaxis)	Grade 4 (Anaphylaxis)	Grade 5 (Anaphylaxis)
Symptoms/signs from 1 organ system	Symptoms or signs from ≥ 2 organ systems	Symptoms from Grade 1 or 2 and	Symptoms from Grade 1-3 and	Symptoms from Grade 1-4
		Lower airway involvement: mild bronchospasm, cough, wheezing And/or	Lower airway involvement Severe bronchospasm and/or	Respiratory failure and/or
		Abdominal cramps and/or	Laryngeal edema and stridor	Cardiovascular Collapse/Hypotension and/or
		Uterine cramps		Loss of consciousness (vasovagal excluded)

Perioperative anaphylaxis

The recent 6th National Audit Project (NAP 6) in the UK defined perioperative anaphylaxis as anaphylaxis which occurs in patients undergoing a procedure requiring general or regional anaesthesia or sedation or managed-anaesthesia care (anaesthesia monitoring only) under the care of an anaesthetist between the period of first administration of a drug (including premedication) and the post-procedure transfer to a ward, or critical care.

Perioperative anaphylaxis is seen as a rare event, with a reported incidence between 1:1250-1:20 000 anaesthetics, equating to on average once every 7 years per anaesthetist. Mortality was previously predicted to be 3-9% but more recent studies in developed nations report is significantly lower ranging from 0-4.1%.

The large number of medications received during a generic general anaesthetic means the risk of iatrogenic anaphylaxis increases significantly during the perioperative period. The Allergen Survey component of NAP6 determined that in a general anaesthetic, a median number of eight drugs were administered, up to a maximum of twenty.

The most common offenders are antibiotics (responsible for 46% of anaphylaxis cases with a known cause in NAP6), NMBA's (33%), Chlorhexidine (9%) and Patent Blue (6.5%). Patent Blue had the highest rate of anaphylaxis per 100 000 administrations. It is important to note that in 72% of anaphylaxis cases in NAP6 no identifiable cause could be established.

Many symptoms of anaphylaxis are difficult to notice under anaesthesia and can lead to delayed recognition. NAP6 detailed the incidence and progression of perioperative anaphylaxis. Hypotension was universally present in all cases of perioperative anaphylaxis and was the presenting feature in half the cases. Bronchospasm/ high airway pressure was present in about 50% of cases, and was the presenting feature in 1 in 5 cases. Urticaria and other rashes were uncommon and often presented late. Upper airway features were seen very rarely. Hypotension and bronchospasm were the most common features associated with fatalities. The first clinical feature appeared within five minutes in two-thirds of cases and within ten minutes in 83% of cases. Most cardiac arrests occurred shortly after initial features were noted.

Follow-up after perioperative anaphylaxis

Evaluation after perioperative anaphylaxis is essential. The patient should be informed of the event and referred for further testing. A detailed clinical report including all drugs given and clinical response as well as management should be completed to aid the investigation.

Histamine

Histamine is a preformed mediator produced by basophils and mast cells and is measured in plasma. It peaks immediately and the half-life is 15-20 minutes so must be measured within thirty minutes to two hours.

Tryptase

Tryptase is a neutral serine protease contained predominantly within mast cells. It peaks between fifteen minutes to two hours after anaphylaxis and the half-life is 90-120 minutes. It should be measured within two to six hours and then compared to baseline tryptase levels measured the next day.

Serum-specific IgE measurement

This is done in vitro and assays are available for a few drugs: including suxamethonium, antibiotics, morphine, chlorhexidine, protamine, latex and the quaternary ammonium group of NMBA's. This is mostly done as part of research and is not commercially available everywhere. Sensitivity and specificity are not high and results should be interpreted in light of the clinical history and skin test results.

Skin testing

Skin testing allows the identification of the culprit agent, the pathophysiological (allergic vs non-allergic) mechanism and safe alternatives. The culprit and cross-reactive drugs identified should be avoided while negative skin-tested drugs can be used subsequently. Mild or moderate anaphylaxis associated with negative skin test and with or without increased histamine or tryptase, suggests a non-allergic mechanism, such as histamine release.

Future management of patient with anaphylactic reaction

Written information regarding the reaction, testing and advice for subsequent anaesthetic management should be available in the hospital notes and copied to the GP, patient and clinicians involved. Patients should wear a warning bracelet or carry a card giving details of the allergy. When anaesthesia is unavoidable after an unexplained or uninvestigated anaphylaxis, the case should be done in a tertiary centre and drugs with a low incidence of hypersensitivity used, such as volatile agents, benzodiazepines, and Remifentanil. Use of inhalation induction or regional anaesthesia should be considered. Avoid chlorhexidine and neuromuscular blocking agents (using Remifentanil) if safe to do so and ensure a latex-free environment. Pre-treatment with corticosteroids and antihistamines does not reliably prevent immune mediated reactions. Full monitoring should be applied and large-bore IV access established.

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Gabapentin and Pregabalin

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Introduction

Pregabalin and gabapentin, collectively known as gabapentinoids, are also known as anticonvulsant drugs. They were initially marketed as anticonvulsants but have subsequently been approved to treat specific chronic neuropathic pain conditions.

Gabapentin was approved by the Food and Drug Administration (FDA) in 1993 for treatment of seizures and subsequently in 2002 for post-herpetic neuralgia—the only pain indication.
Pregabalin was FDA–approved in 2004 for neuropathic pain (diabetic neuropathy and post-herpetic neuralgia), then fibromyalgia (2007), and spinal cord injury neuropathic pain (2012). They differ only in their pharmacokinetics.

In South Africa they are licensed to be used for the treatment of pain associated with post-herpetic neuralgia and painful diabetic polyneuropathy.

Since their release they have however been increasingly used off label for non-neuropathic pain conditions- both acute and chronic. This has been partly due to prescribers trying to avoid opioids- and to a certain degree- a belief that this drug works in other neuropathic pain conditions such as compressive neuropathy like sciatica. There is however very little evidence for its use outside these of these indicated conditions.

These are two very useful articles which review the off- label and acute pain use of the gabapentinoids:

Off- label use review:

Goodman CW, Brett AS. **A clinical overview of off-label use of gabapentinoid drugs**. JAMA intern Med. 2019; 179(5):695–701. DOI:10.1001/jamainternmed.2019.0086**.**

Acute pain use review:

Verret M, Lauzier F, Zarychanski R, et al. **Perioperative Use of Gabapentinoids for the Management of Postoperative Acute Pain: A Systematic Review and Meta-analysis** *Anesthesiology*. 2020; 133(2):265-279. doi:10.1097/ALN.0000000000003428

Mechanism of action

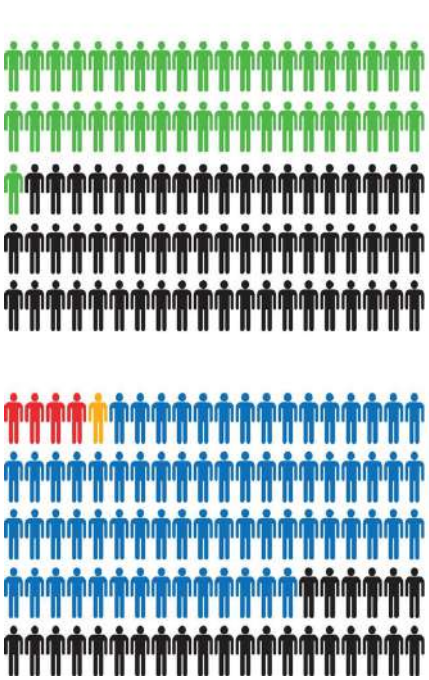
It is important to realise that the gabapentinoids do not work as GABA agonists. They bind to the α2-delta subunit of voltage gated calcium channels in the dorsal horn of the spinal cord and peripheral nerves. This results in a decrease of excitatory neurotransmitter (glutamate, noradrenaline and substance P) release from activated nociceptors, inhibits ascending pain transmission, activates descending inhibitory pathways, and prevents hyperalgesia and central sensitization. This is believed to contribute to their anticonvulsant, analgesic, and anxiolytic actions.

Indications

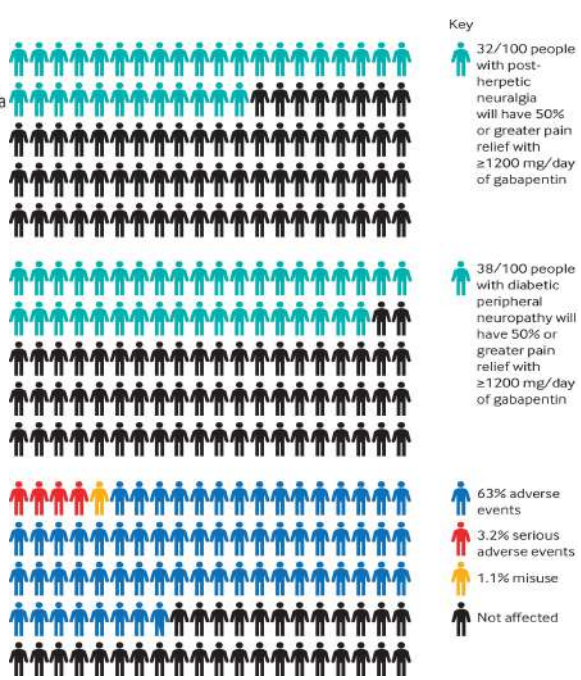
Pain associated with post-herpetic neuralgia and painful diabetic neuropathy

How well do they work?

Pregabalin



Gabapentin



Mathieson S, Lin Chung-Wei C,Underwood M, Eldabe,S. Pregabalin and gabapentin for pain BMJ 2020; 369 :m1315

Fibromyalgia

One in 10 patients with moderate to severe fibromyalgia taking pregabalin (300-600 mg daily) experiences a 30-50% reduction in pain over 12 to 26 weeks, based on high quality evidence from a Cochrane review.

Other conditions

Systematic reviews have found no treatment benefits of gabapentinoids over placebo in low back pain, sciatica, and spinal stenosis or episodic migraine in adults. Evidence to support the use of pregabalin in acute pain, HIV neuropathy, neuropathic cancer pain, and other forms of neuropathic pain, is insufficient.

Contraindications and cautions: known hypersensitivity to these drugs and reduced renal clearance (check elderly renal function)

Drug Interactions: Alcohol and other CNS depressants- may cause additive impairment of cognitive and motor function.

Pharmacokinetics:

Parameter	Pregabalin	Gabapentin
Oral bioavailability	>90% independently of the dose	<50% dependently of the dose
Absorption	Non-saturable	Saturable
Protein binding	No/Minimal	Minimal
Time to maximum plasma concentration	1 h	2-3 h
Metabolism	Not metabolized by cytochrome P450 enzymes Renally excreted, 98% unchanged	Not metabolized by cytochrome P450 enzymes Renally excreted
Plasma half-life	6.3 h	5-9 h
Drug interactions	No significant drug interactions reported	Antacids decreased the oral bioavailability of gabapentin by 20-30%
Titration	Maximal dose achieved within a few days	Over several weeks to attain maximal tolerated dose
Starting dose	75-150 mg/day	100-900 mg/day
Maximal dose	Up to 600 mg/day	Up to 3,600 mg/day
Administration	Twice/three times daily	Three times daily

Modified from Chiechio S, et al. Pregabalin in the treatment of chronic pain: an overview. Clin Drug Investig 2009;29:203-13

Adverse effects

Because the gabapentinoids bind to the α-$_2$-δ subunit of voltage-gated calcium channels, which are richly expressed in the cerebellum and hippocampus, they cause dizziness, balance disorders, ataxia, visual disturbances, sedation, somnolence, and cognitive impairment.

Early perioperative gabapentinoid studies focused on analgesia but not side effects. In retrospect, however, there were early and clear yet underappreciated signals of side effects, most notably dizziness and sedation. Years later, it is now clear that perioperative gabapentinoids are associated with a greater risk of sedation, dizziness, and visual disturbances. It is perhaps paradoxical that enhanced recovery protocols, which endeavour to avoid these very complications of sedation, somnolence, and cognitive impairment that can delay recovery, can advocate the routine use of gabapentinoids.

More importantly, pregabalin use was associated with a nearly three-fold greater relative risk of serious adverse events (life-threatening; resulting in death, disability, or significant loss of function; or causing hospital admission or prolonged hospitalization). Day-of-surgery gabapentinoid use was associated with dose-dependent increased odds of postoperative pulmonary complications (respiratory failure, pneumonia, reintubation, pulmonary oedema, non-invasive ventilation, or invasive mechanical ventilation) and intensive care unit admission and without decreased opioid requirements or length of stay.

Dose

Adult: Oral, 75mg twice daily- some clinicians advocate for a nocte dose only or a reduced morning dose- e.g. 25mg mane/ 75mg nocte to reduce side effects.

Can increase to 150mg bd – even up to 300mg bd. Generally after an interval of 3- 7 days.
Reduce dose in renal failure- see SAMF

Preparations: 25mg, 75mg, 150mg tablets

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Notes

Antibiotic Resistance
(and other concepts)

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Resistance to antibiotics occurs when bacteria develop (or already possess) the ability to avoid the mechanisms which the antibiotics use to destroy them. Antibiotic resistance results in increased morbidity and mortality since the antibiotic-resistant pathogens are generally more difficult to treat. This is of grave concern, as it is estimated that, globally, 700 00 people die each year because of antibiotic-resistant bacteria, and projections suggest this will rise to 10 million deaths annually by 2050. Aside from the impact on mortality, infections from multidrug resistant (MDR) organisms are associated with an increased duration of hospital stay and, as such, have an adverse economic impact.

Antibiotics are amongst the most commonly prescribed medications, yet it is estimated that about 50% of their use is unnecessary, and is a chief driver of antimicrobial resistance. Although misuse of antibiotics is not limited to medicine (it is also widespread in animal husbandry, farming and industry) iatrogenic causes of antibiotic resistance remain a grave concern. The role we play in driving resistance includes inappropriate dosing, inappropriate use, and lack of knowledge of pharmacokinetics and dynamics. Resistance can be iatrogenically driven by:

- Using antibiotics when they are not indicated
- Using the wrong antibiotic with poor activity against the microorganism
- Using broad spectrum antibiotics inappropriately
- Under-dosing
- Using too short or too long a course of therapy
- Choosing an antibiotic that has poor effect site penetration
- Being unaware of the PK/PD and the optimal dosing strategy.

These notes will cover bacterial resistance mechanisms, optimal prescribing, the principles behind good antibiotic stewardship…as well as a few other bits that are important for the exam, and to make you a better doctor!

1. Classes of antibiotics and when to use them

Below, is a brief overview of some of the commonly used antibiotics in clinical practice, in South Africa. Although not necessarily relevant in the subject of antimicrobial resistance, this is a topic registrars (and consultants) ***always*** ask – which antibiotics cover which bugs…often something that is very difficult to answer, and a huge section in its own right.

1.1 Drugs which inhibit cell wall synthesis

These include the ß-lactams and glycopeptides.

1.1.1 ß-lactams

ß-lactams are antibiotics which include a ß-lactam ring in their chemical structure. They are the most commonly used class of antibiotic and have hydrophilic properties (the importance of this is covered in the section of dosing in the critically ill patient). ß-lactam antibiotics include: *Penicillins* and *penicillin derivatives* (e.g. *amoxicillin, piperacillin*), c*ephalosporins*, *monobactams* and *carbapenems.* All the ß-lactams are excreted in the urine.

ß-lactam antibiotics exert their bacteriocidal effects through binding to penicillin binding proteins (PBP). PBPs are bacterial enzymes which are responsible for cross-linking of peptidoglycans and are necessary to maintain the integrity of the bacterial cell wall. ß-lactam antibiotics therefore inhibit PBPs, which weakens the peptidoglycan layer, causing the cell to lyse due to osmotic pressure. Because ß-lactams interfere with bacterial cell wall synthesis, they are ineffective against bacteria which do not

possess a cell wall (such as *Mycoplasma*). Being hydrophilic, they are also ineffective against intracellular pathogens (such as *Chlamydia*, *Brucella* or *Legionella*) and pathogens with impenetrable cell walls (such as *Mycobacteria*).

- *Penicillins*

The natural penicillins (e.g. benzylpenicillin / penicillin G, and phenoxymethylpenicillin / penicillin V) have a narrow spectrum of activity and resistance is common. Penicillin derivatives have been developed to improve features such as spectrum of activity, bioavailability, stability etc. The first major development was that of ampicillin in 1961 followed by ß-lactamase-resistant penicillins (e.g. methicillin, flucloxacillin) and antipseudomonal penicillins (e.g. piperacillin), which have a broader coverage against Gram-negative organisms.
(Note: Piptazobactam is a combination of piperacillin and tazobactam, it has good activity against Gram-positive, Gram-negative and anaerobic microorganisms). See Table 1.

Table 1. Classification and spectrum of antimicrobial activity of penicillins

Penicillin	Category	Spectrum of activity
Penicillin G / V	Natural penicillin	Gram-positive bacteria
Cloxacillin, oxacillin	Semi-synthetic, ß-lactamase resistant	Gram-positive bacteria
Amoximcillin, ampicillin	Semi-synthetic, amino penicillin	Gram-positive bacteria e.g. *Listeria monocytogenes* Gram-negatives including *Escherichia coli, Proteus mirabilis*
Piperacillin	Semi-synthetic, ureido penicillin	Gram-positive bacteria Improved Gram-negative coverage including *Klebsiella* spp. and *Pseudomonas*

- *Cephalosporins*

These ß-lactam antibiotics are frequently grouped into "generations" depending on their antimicrobial effects, although exact categorisation may vary between countries. By and large, each subsequent generation of cephalosporin has greater Gram-negative cover than the preceding generation, and *usually* less activity against Gram-positive organisms (see Table 2). Cefamycins are a group of antibiotics which belong to the second generation cephalosporins – these include cefoxitin and cefotetan and are a little different from their cephalosporin buddies as they have anaerobic cover and their modified structure makes them resistant to the effects of ESBLs (see section 2.2).

Table 2. Classification and spectrum of antimicrobial activity of cephalosporins

Generation	Examples	Spectrum of activity
First	Cefazolin Cefadroxil	G+ (no activity against Methicillin-resistant *Staphylococcus aureus - MRSA*) G- some *Proteus mirabilis*, *E. coli* and *Klebsiella pneumonia* (PEcK). No effect against *Pseudomonas, Enterobacter, Serratia, Acinetobacter*
Second	Cefuroxime Cefoxitin Cefotetan	Less G+ effect than 1st generation More G- effect than 1st generation (e.g. against *Haemophilus influenza, Enterobacter* spp.) Cefoxitin and Cefotetan have anaerobic effects
Third	Ceftriaxone Cefotaxime Ceftazidime	Less G+ effect (compared to 1st and 2nd generation cephalosporins) More G- effect, including nosocomial sepsis (no effect against Extended-spectrum ß-lactamases) Penetrate central nervous system No activity against anaerobic organisms
Fourth	Cefepime	G+ effect like 1st generation cephalosporins G- antipseudomonal effects; more resistant to ß-lactamases than 3rd generation No activity against anaerobic organisms
Fifth	Ceftobiprole Ceftaroline	Ceftobiprole has good effect against *Pseudomonas* spp. and Vancomycin Resistant Enterococci (VRE) Ceftaroline has activity against MRSA but no antipseudomonal or VRE effect

- *Monobactams*

e.g. Aztreonam
Possess activity against Gram-negative organisms only.

- *Carbapenems*

Carbapenems are ß-lactam antibiotics with a broad spectrum of activity, and are usually reserved for nosocomial or MDR pathogens. They are particularly effective against Gram-negative organisms, (but their Gram-positive effects are slightly narrower) and they possess anaerobic activity. In addition to the spectrum of activity highlighted in table 3, the carbapenems do not have activity against atypical microorganisms (e.g. *Chlamydia, Legionella, Mycoplasma*).

Carbapenems are divided into 3 groups according to their spectrum of activity (see Table 3).

Table 3. Classification of carbapenems and spectrum of activity

Group	Examples	Spectrum of activity
1	Ertapenem	Broad spectrum Limited activity against non-fermentative Gram-negative bacilli (e.g. *Acinetobacter, Pseudomonas, Burkholderia, Stenotrophomonas*) No activity against MRSA or *Enterococcus* spp. Half-life 4 hours
2	Imipenem Meropenem Doripenem	Broad spectrum. Activity against non-fermentative Gram-negative bacilli. No activity against MRSA. Half-life ±1 hour
3	None currently licensed for clinical use	Broad spectrum MRSA activity

The carbapenems diffuse poorly through the Gram-negative outer cell membrane so are reliant upon porins (outer membrane proteins) to facilitate their passage into the cell. Once inside the bacteria, carbapenems bind to PBPs and weaken peptidoglycans, rendering the cell wall less resistant to osmotic stress.

Imipenem is deactivated in the kidneys by the enzyme dehydropeptidase-1 (DHP-1), to overcome this deactivation, it is administered with the DHP-1 inhibitor, cilastatin. Imipenem is frequently described as having the potential to induce seizures, but bear in mind that this is not only a side-effect of imipenem – all the ß-lactam antibiotics can cause seizures, especially when administered in high doses. Imipenem has slightly better activity against Gram-positive bacteria compared to meropenem; meropenem is slightly more effective against Gram-negative organisms compared to imipenem. Ertapenem has a more limited spectrum of activity than the Group 2 carbapenems as it is ineffective against *Pseudomonas aeruginosa* and *Enterococcus* spp.

Side effects of the ß-lactams include neurotoxicity (seizures, spasms, hallucinations) as well as the well-known hypersensitivity reactions.

1.1.2 *Glycopeptides*

e.g. Vancomycin and Teicoplanin
Glycopeptides have activity against Gram-positive organisms. They are large molecules, and thus are unable to penetrate the outer membrane of the Gram-negative organisms. Like the ß-lactams, they interfere with cell-wall synthesis, although act at an earlier stage of synthesis than the ß-lactams.

Resistance to the glycopeptides is also well described, especially in *Enterococci species* (*Enterococcus faecium* and *faecalis*), Vancomycin-resistant Enterococci (VRE) and Coagulase-negative staphylococci (CNS). Coagulase-positive staphylococci (e.g. *Staphylococcus aureus*) may also demonstrate reduced susceptibility to the glycopepetides (e.g. Vancomycin-Intermediate Staphylococcus Aureus (VISA) and Glycopeptide-Intermediate Staphylococcus Aureus (GISA)).

Side effects of the glycopeptides include ototoxicity and nephrotoxicity (although the renal toxic effects of vancomycin are over-exaggerated; however, vancomycin accumulates in renal failure and serum drug level monitoring is recommended). Rapid infusion of vancomycin can cause histamine release, resulting in “red-man syndrome”

1.2 Antibiotics which inhibit protein synthesis

These include the aminoglycosides and tetracyclines (which bind to the 30S ribosomal subunit), chloramphenicol, macrolides, lincosamides, streptogramins, oxazolidinones (which bind to the 50S ribosomal subunit), and fusidic acid ….I will only deal with the most clinically relevant ones, otherwise I'll be here forever!

1.2.1 Aminoglycosides

e.g. Gentamycin, Amikacin, Tobramycin
This important group of antibiotics is administered via the intravenous route, since these drugs are poorly absorbed from the gut. Importantly, they have poor tissue and lung penetration so are not very good for treating pneumonia. However, the use of nebulized aminoglycosides (**in addition to** targeted intravenous therapy) is finding favour due to the extremely high concentration of antibiotic in the alveolar fluids which this mode of delivery yields. Aminoglycosides have no activity against anaerobes or streptococci, but have good activity against Staphylococci and excellent activity against Gram-negative organisms. Side-effects of aminoglycosides include nephro- and oto-toxicity. They have a narrow therapeutic window.

Aminoglycoside-modifying enzymes (AME) are an important mechanism of resistance to this class of antibiotics. The enzymes inactivate the drug by altering the structure of the aminoglycoside (see section on mechanisms of resistance).

1.2.2 *Macrolides*

e.g. Erythromycin, Clarithromycin, Azithromycin
Erythromycin deserves a mention here; not for its antimicrobial use in ICU, but for its increasing use as a prokinetic to facilitate enteral feeding. The dose for prokinesis is much smaller than that used for treatment of microbial infections (prokinetic dose 250mg 6 hourly, intravenously); its antimicrobial action is against Gram-positive organisms (and is often used in patients who are allergic to penicillin compounds).

Clarithromycin and azithromycin (as well as erythromycin) have excellent activity against atypical microorganisms (*Legionella, Chlamydia, Rickettsia, Brucella*) and have an important role in the treatment of severe community acquired pneumonia.

1.2.3 *Lincosamides*

e.g. Clindamycin
Clindamycin has a similar spectrum of activity to erythromycin, but has better anaerobic cover. It has excellent penetration into the bone and soft tissue, but received bad press as it was the first antibiotic to be implicated in causing pseudomembranous colitis.

1.2.4 Oxazolidinones

e.g. Linezolid
Linezolid is a bacteriostatic antibiotic with activity against a wide-range of Gram-positive bacteria (including MRSA and *Enterococcus faecium*). Linezolid may be associated with a worse outcome (compared to Daptomycin) when used to treat blood stream infections caused by Vancomycin-resistant enterococci (VRE).

1.3 Antibiotics which inhibit nucleic acid synthesis

1.3.1 Quinolones

e.g. Nalidixic acid, Ciprofloxacin, Moxifloxacin, Levofloxacin
The quinolones interfere with the replication of the bacterial chromosome. They have Gram-positive and good Gram-negative activity. Moxifloxacin and levofloxacin have some activity against anaerobes. Side effects include neurotoxicity and photosensitivity; caution is advised in the use of quinolones during pregnancy and in children due to their adverse effect on cartilage development. Quinolone-associated tendinitis and tendon rupture is more likely in the elderly, as well as in patients with renal

impairment, solid organ transplants and those taking corticosteroids. A recent safety warning has emerged with the recognition of quinolones being associated with aortic aneurysms and dissection.

1.3.2 Rifamycins

e.g. Rifampicin
Rifampicin blocks the synthesis of bacterial mRNA. It is primarily used for the treatment of Mycobacterial infections. Side-effects includes hepatic dysfunction and skin rashes. In our setting, rifampicin is seldom used other than for the treatment of tuberculosis, due to the increased risk of collateral damage with the development of rifampicin-resistant-TB, in a setting where TB prevalence is very high.

1.4 Antibiotics which inhibit metabolic pathways

1.4.1 Sulfonamides

e.g. Sulfamethoxazole is a bacteriostatic antibiotic which competes with *para*-aminobenzoic acid (PABA), an enzyme involved in the catalysis of tetrahydrofolic acid (THFA) (which is required for the synthesis of purines and pyrimidines). Sulfonamides may cause Stevens-Johnson syndrome.

1.4.2 Trimethoprim

Trimethoprim prevents synthesis of THFA, but does so at a later stage of the pathway than sulfamethoxazole. Trimethoprim has activity against Gram-negative bacteria (but no activity against *Pseudomonas* spp).

Sulfamethoxazole and trimethoprim are often administered as the combination agent co-trimoxazole. The combination of the 2 drugs is synergistic and is valuable in the treatment of *Pneumocystis jirovecii* and *Nocardia*.

1.5 Antibiotics which depolarise the cell membrane

1.5.1 Lipopeptides

e.g. Daptomycin is a cyclic lipopeptide antibiotic with bactericidal activity against Gram-positive organisms including resistant strains (i.e. MRSA, GISA, VRE and coagulase-negative *Staphlococcus* spp.). The novel mechanism of action involves the lipophilic tail of the molecule inserting into the bacterial cell membrane, causing rapid depolarisation and efflux of potassium ions. DNA, RNA and protein synthesis are arrested and the bacteria dies. Daptomycin has excellent penetration in to skin and soft tissues, but does not cross the blood-brain barrier. It is not metabolized by hepatic enzymes.

1.6 Other commonly used antibiotics

1.6.1 Nitroimidazoles

e.g. Metronidazole. For metronidazole to destroy bacterial DNA, the parent compound must enter the bacterial cell, which requires activation by reduction. Anaerobic organisms have the ability to produce a low redox potential for the reduction and activation of metronidazole. As such, metronidazole has activity against anaerobic organisms, and no activity against aerobic bacteria. Metronidazole also has anti-parasitic effects; it is used in high doses for the treatment of amoebic liver abscesses.

1.6.2 Polymixins

e.g. Colistin (Polymixin E).
The polymixins disrupt the cell membrane and have good activity against Gram-negative bacteria. *Proteus* spp. is inherently resistant to the polymixins. In our clinical setting Colistin is commonly used for infections due to pan-drug-resistant *Acinetobacter baumanii*. Side effects include nephrotoxicity and neurotoxicity.

2. Mechanisms of resistance

2.1 Classification of antibiotic resistance

Antimicrobial resistance can be classified as intrinsic, acquired (or induced), or adaptive.

2.1.1 Intrinsic resistance

Intrinsic resistance is when bacteria are innately / intrinsically resistant to antibiotics. Even if the antibiotic concentration is given in enormous doses there will be no effect on the specific bacteria. E.g.

- Vancomycin has no effect on Gram-negative bacteria because the outer membrane of the Gram-negative bacterial cell envelope is impermeable to glycopeptides
- *Serratia* spp., *Burkholderia* spp. and *Proteus* spp. are all intrinsically resistant to Colistin
- *Enterococci* spp. are intrinsically resistant to cephalosporins and aminoglycosides
- *Klebsiella* spp. are intrinsically resistant to ampicillin
- *Pseudomonas* spp. are intrinsically resistant to ampicillin and the 1st and 2nd generation cephalosporins.

Intrinsic resistance universally occurs within a species of bacteria. It is independent of prior exposure to antibiotics and is not due to horizontal gene transfer, but is an inherent property of the bacteria. The commonest mechanisms resulting in intrinsic resistance are: reduced permeability of the outer cell membrane, and the activity of efflux pumps (see below for a more detailed explanation).

2.1.2 Acquired resistance

A bacterium may develop or acquire resistance (after having been previously susceptible); this is also termed **induced resistance**. This may arise from

- Chromosomal mutations
    - Single spontaneous chromosomal mutation
    - Multiple spontaneous chromosomal mutations
- Introduction of new genetic material into the bacterium
    - Horizontal transfer of resistant genes on plasmids, transposons, phages or cassettes are inserted into the bacteria's DNA. The acquisition of exogenous genetic material may be temporary or permanent and occurs due to transformation, transduction or conjugation

2.1.3 Adaptive resistance

Adaptive resistance is induced by environmental stressors (e.g. sub-inhibitory levels of antibiotics, changes in pH etc.). The stressors do not cause an alteration in the genetic makeup and are likely due to epigenetic changes. Unlike intrinsic or acquired resistance, adaptive resistance is usually (but not always!) transient, and disappears once the signal is removed. Adaptive resistance may explain the differences in the *in vivo* and *in vitro* efficacy of antibiotics, and why there may be clinical failure despite good *in vitro* activity.

2.2 Mechanisms of antibiotic resistance

The mechanisms by which resistance occurs is divided into 3 main types:

1. Alteration of the target site where the antibiotic acts; e.g. alteration of structure of the Penicillin Binding Protein (PBP). This means that the antibiotics are unable to bind effectively to the PBP and don't effectively interrupt cell wall synthesis. Methicillin-resistant *Staphyloccus aureus* (MRSA) is an example of a bacteria which uses this mode of resistance. Although mercifully rare in South Africa, Vancomycin-resistant *Staphylococcus aureus* (VRSA) and Vancomycin-resistant enterococci (VRE) are resistant to vancomycin because the target for binding of the glycopeptides is modified, thereby reducing the binding affinity.
2. Alteration of antibiotic access to the target site (altered uptake or increased elimination of the drug)
    a. Gram-negative organisms possess an outer membrane with low permeability for many antibiotics, this is an important mechanism of intrinsic resistance of some Gram-negative bacteria. Hydrophilic compounds gain access to the cell through channels in

the bacterial outer membrane called porins. Mutations in the porin gene causes repression of porin channels which decreases the permeability of the outer membrane to the antibiotic, rendering the antibiotic ineffective as it is unable to gain access into the bacteria.

b. Energy-dependent efflux pumps are situated on the cytoplasmic membrane. The function of efflux pumps is to pump toxic substances out of the bacterial cell. Many of them can transport a large variety of compounds and drugs, including antibiotics. This is an important mechanism Gram-negative resistance to tetracylines as well as carbapenems.

Note, because Gram-positive bacteria do not possess a lipopolysaccharide outer membrane, they do not effectively limit drug uptake (i.e. porin-type mechanisms of resistance) and similarly are unable to utilise some of the drug efflux mechanisms.

3. Production of enzymes which inactivate, destroy, or modify the antibiotic agent
    a. ß-lactamases, Extended-Spectrum ß-lactamases (ESBLs), Carbapenemases. These destroy ß-lactam antibiotics.
    b. Aminoglycoside modifying enzymes (AME). These modify and inactivate antibiotics, but do not destroy them. The modified antibiotic has a decreased avidity for its site of action.

ß-lactamases deserve a special mention as they are the commonest mechanism of resistance against ß-lactam antibiotics among Gram-negative bacteria. They are commonly classified by the Ambler classification which was proposed in 1980. According to the Ambler classification, the β-lactamases were divided into four classes based on their sequence similarity. Classes A, C and D possess a serine ester involved in hydrolysis, whereas class B β-lactamases, also known as metallo-β-lactamases, have a zinc ion as a cofactor in catalysis. The β-lactamases produced by Gram-positive bacteria are mainly from group A. Although interesting, the Ambler classification is outside the scope of required knowledge for the FCA!!

- ß-lactamase enzymes hydrolyse the ß-lactam ring, causing the ring to open. Drugs with an open ring are unable to bind to the target PBP site and are therefore ineffective. Fascinatingly, ß-lactamases were first described in 1940, 1 year before penicillin was introduced into clinical practice!
- Inducible ß-lactamases (IBL) are cephalosporinases. In IBL-producing organisms (such as *Enterobacter* spp*., Serratia* spp*., Pseudomonas aeruginosa)* the expression of ß-lactamase is usually repressed, but in the presence of selected ß-lactam antibiotics (particularly 3rd generation cephalosporins) the production of the enzyme is greatly increased. This can lead to the rapid emergence of resistance to multiple ß-lactam antibiotics. ß-lactamase inhibitors (e.g. clavulanic acid, sulbactam, tazobactam, avibactam) are molecules which contain a ß-lactam ring but have little bactericidal activity. When combined with a ß-lactam antibiotic they act as "suicide inhibitors" by binding to the ß-lactamase enzyme and preventing the ß-lactam antibiotic from being hydrolysed. For example, Co-amoxyclav is made up of amoxicillin (a ß-lactam antibiotic) and clavulanic acid (a ß-lactamase inhibitor) which prevents amoxicillin being inactivated by the ß-lactamase enzyme. Similarly, piperacillin-tazobactam combines the ß-lactam antibiotic piperacillin, with tazobactam (a ß-lactamase inhibitor).
- Extended-spectrum ß-lactamases are ß-lactamases produced by *Enterobacteriacae,* which confer resistance to many ß-lactam antibiotics (penicillins, cephalosporins and monobactams) but not to carbapenems. They are Class A ß-lactamases, according to the Ambler classification. Carbapenems are the antibiotic of choice if the bacteria produce ESBLs; ertapenem is recommended as it has the narrowest spectrum of activity, but some ertapenem-resistant isolates have been reported. Although (occasionally) some of the later generation cephalosporins may appear to be effective against such organisms *in vitro*, the use of these antibiotics is associated with a high treatment failure rate *in vivo*. As an oddity, the cephamycins (such as cefotetan and cefoxitin) are resistant to the effects of ESBLs.
- Carbapenemases have activity against the penicillins, cephalosporins and carbapenems. The carbapenems have been the "go-to" class of antibiotics for nosocomial sepsis for many years as they are relatively resistant to hydrolysis by most ß-lactamases. However, in recent years, the emergence of carbapenemase enzymes which destroy the carbapenem threatens their successful antimicrobial profile, especially their activity against Enterobacteriacae - termed *Carbapenem-resistant Enterobacteriales* (CRE). KPC (*Klebsiella pneumoniae* carbapenemase – Ambler Class A), the metallo-ß-lactamases VIM (Verona integron encoded metallo-ß-lactamase – Ambler class B) and NDM-1 (New Delhi metallo-ß-lactamase – Ambler

class B) and Oxacillinases (e.g. OXA-48 – Ambler class D) are all examples of enzymes which destroy carbapenems and are spread by plasmids across a wide spectrum of bacteria. Ceftazidime-avibactam is a relatively new combination drug (the 3rd generation cephalosporin ceftazidime plus avibactam, a ß-lactamase inhibitor) which has activity against CREs.

[Plasmids are molecules of DNA which exist outside of the chromosomal DNA. They are readily passed between bacteria, and frequently express enzymes which confer resistance to more than 1 antibiotic].

Risk factors for developing resistant infections (e.g. CREs) include cumulative antibiotic exposure – this includes not only the number of previous exposures to antibiotics, but also long duration of treatment "courses". This will be further covered in the section on Antimicrobial Stewardship (Section 5).

Biofilm

Biofilm deserves a special mechanism as an important tool in bacterial colonization. The secretion of a biofilm by a bacterial colony prevents detection from the host's immune system, and the thick and sticky consistency of the matrix retards penetration by antimicrobials – a much higher concentration of antibiotic is required to penetrate through the biofilm. Within the colony, the bacteria tend to be sessile (slower metabolic rate and cell division) minimising the effect of antimicrobials that target bacterial growth; horizontal gene transfer is also facilitated throughout the densely-packed colony.

3. Microbiological speak

Deciding on which antibiotic to use against which microbe depends on many factors:

- Susceptibility of the organism to the antibiotic
- Effect site concentration
- Collateral damage and side effects
- Pharmacokinetic and pharmacodynamic (PKPD) principles

3.1 Susceptibility of the organism to the antibiotic

The ***minimum inhibitory concentration (MIC)*** **is the lowest concentration of an antibiotic (in µg/mL) that inhibits the growth of a strain of bacteria.** Quantifying the result can help to determine which antibiotic is most effective against the bacteria (the lower the MIC, the more likely an organism will be susceptible to a particular antibiotic). However, the MIC must be compared to the **breakpoint** (see below) to describe whether the bacteria is Resistant, Sensitive or Intermediate when the antibiotic is administered in "usual doses".

The MIC for one antibiotic cannot be compared to an MIC for another antibiotic, as this relies on other information such as the antibiotic ***breakpoint*** and the site of infection etc. The **breakpoint is a previously agreed upon concentration of antibiotic which defines whether a species of bacteria is susceptible or resistant to the antibiotic** i.e. where bacteria begin to show resistance. If the MIC is less than, or equal to the breakpoint, then the bacterial isolate is reported as being susceptible / sensitive to the antibiotic. Breakpoints are predetermined by national organisations (e.g. EUCAST in Europe and CLSI in the USA). These data are published and updated annually. By way of example: a strain of *Klebsiella pneumonia* has MICs of 2µg/mL for piptazobactam, 2µg/mL for cefepime and 2µg/mL for gentamycin. Although the MICs are the same, it does not necessarily mean that the *Klebsiella pneumonia* will be equally susceptible to all three agents. The closer the MIC is to the breakpoint, the less susceptible the organism. If, in the above example the MIC breakpoint for piptazobactam is 8, cefepime is 1 and gentamycin is 2, then the *Klebsiella* will be most susceptible to the piptazobactam and will be least susceptible to cefepime.

The term resistant implies that "normally" achievable serum drug levels are inadequate to inhibit bacterial growth. Intermediate implies that organisms are likely to be inhibited only if maximally recommended doses are used to achieve serum concentrations. Organisms which are resistant or have intermediate sensitivities may still be susceptible if high concentrations of the antibiotic are achieved, for example gentamycin achieves high concentrations in the urine, and may be sufficiently high to treat a lower urinary tract infection caused by an organism reported as gentamycin-resistant.

Mutant Prevention Concentrations (MPC) is a pharmacodynamic concept which highlights the importance of achieving high levels of antibiotic to prevent the development of microbial mutations and the emergence of resistant organisms. MPC is defined as the concentration of antibiotic that prevents the growth of single step mutations. This means that, above the MPC, microbes need to mutate more than once to develop resistance (i.e. makes the development of resistance less likely). Dosing in the concentration window between the MIC and the MPC encourages mutations and selects for resistant organisms. This is termed the Mutant Selection Window (MSW) and is the difference between the MPC and MIC. See Figure 1.

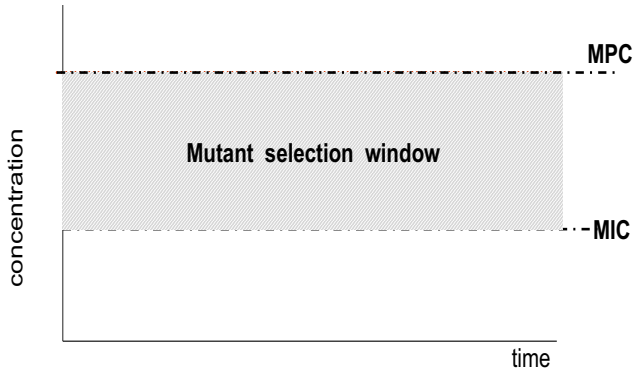


Figure 1. Cartoon to demonstrate the relationship between MIC, MPC and MSW.

3.2 Effect site concentration

It is not possible to measure the drug level at a microbe level, so surrogate levels of the drugs are used instead, i.e. the concentration of the drug in serum or in tissue. Some knowledge about the penetration of the antibiotic at the site of infection is important when prescribing such agents. For example, some drugs (e.g. the aminoglycosides) have poor penetration in to the lung parenchyma and alveolar fluid, and are unsuitable for treating pneumonia. However, if aminoglycosides are delivered by nebulisation, the extremely high doses generated in alveolar fluid may be sufficient to kill the bacteria, even those which are relatively resistant. Similarly, large doses of ceftriaxone and meropenem have good penetration into cerebrospinal fluid (CSF), whereas ertapenem and vancomycin have poor penetration and are unsuitable for systemic use in infections of the central nervous system (CNS). See Table 4.

Table 4. Target tissue penetration by commonly used antibiotics (taken from South African Antibiotic Stewardship Programme: A pocket guide to antibiotic prescribing for adults in South Africa 2015. Wasserman, Boyles and Mendelson)

Antibiotic	CSF	Lung	Soft tissue	Urinary tract
Co-amoxyclav	Poor	Good	Good	Fair
Ceftriaxone	Good (in high dose)	Good	Good	Good
Aminoglycosides	Poor	Poor	Fair	Good
Co-trimoxazole	Good	Good	Good	Good
Ertapenem	Poor	Good	Good	Good
Meropenem	Good (in high doses)	Good	Good	Good
Imipenem	Good	Good	Good	Good
Vancomycin	Poor	Fair	Poor	Good

Therapeutic drug monitoring (TDM) is the measurement of specific drugs (in this case antibiotics) at designated time intervals to optimise individual dosing regimens, and achieve required PK/PD targets. However, most TDM measures serum / blood concentrations, which may not reflect the concentration at the effect site.

3.3 Collateral damage

Collateral damage is the term describing unintended adverse effects on the ecology due to antibiotic use which manifests as the selecting out of, and development of colonization with, MDR pathogens. The use of broad spectrum agents such as third generation cephalosporins and quinolones have been linked to the development of bacterial resistance. Quinolones are linked to the development of

methicillin-resistant *Staphylcoccus aureus* (MRSA) and an increase in the resistance of *Pseudomonas aeruginosa*; 3rd generation cephalosporins are linked to the development of subsequent infections with *Clostridium difficile*, VREs, resistant *Acinetobacter baumanii* and ESBL-producing *Klebsiella pneumoniae.*

Clearly, one must also be cognisant of the side effects of the antibiotics as well as the patient's clinical condition, for example: avoiding nephrotoxic agents in patients with renal dysfunction.

3.4 Pharmacokinetic / pharmacodynamic properties

Antibiotics exhibit optimal antibacterial effects based on pharmacokinetic (PK) and pharmacodynamics (PD) principles; the dose and dosing interval of the antimicrobial is determined by these PKPD relationships. Antibiotics are broadly classified into one or more of the following categories in terms of the relationship between dose and concentration (See Figure 2 – this will be explained fully later in the text):

a) time-dependent (t >MIC)
b) concentration dependent (C_{max}/MIC)
c) a combination of a and b, expressed as the area under the concentration-time curve (AUC_{0-24h}/MIC).

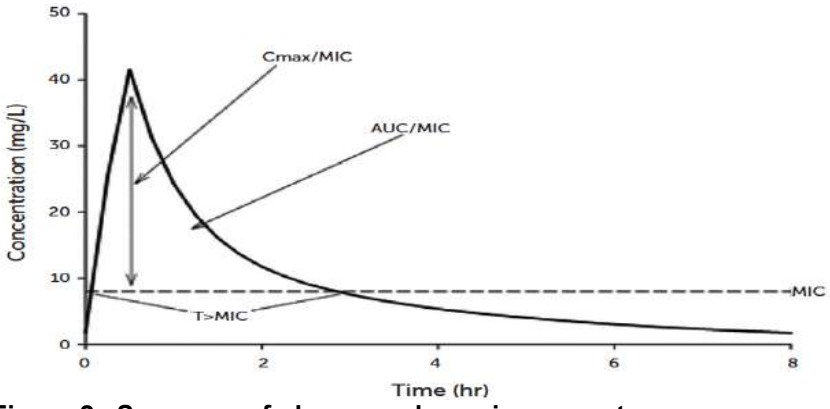


Figure 2. Summary of pharmacodynamic parameters over a concentration time profile

Examples of which antibiotics belong to which PKPD class are given in Table 5 (adapted from Blot SI et al. Advanced drug delivery reviews 2014; 77:3-11).

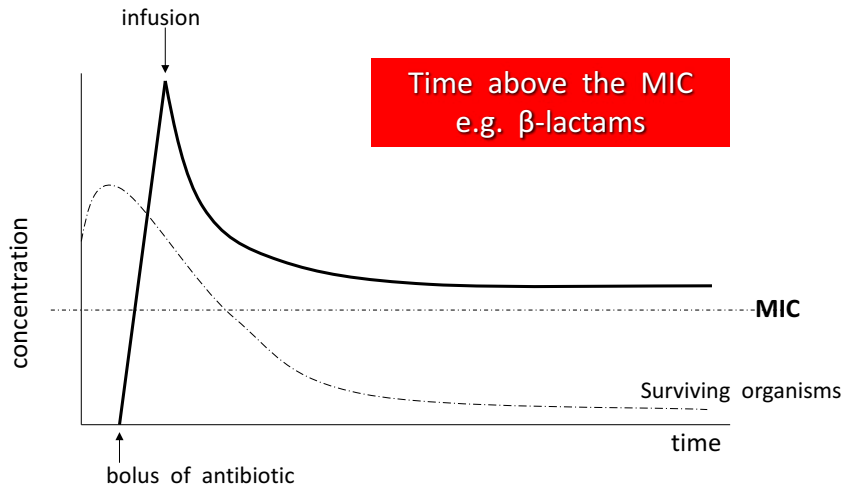
Table 5. Pharmacokinetic and pharmacodynamic properties of commonly used antibiotics

	Time-dependent (t>MIC)	**Concentration-dependent (C_{max}/MIC)**	**Concentration AND time dependent (AUC_{0-24h}/MIC)**
Objective	Maximise duration of exposure	Maximise concentration	Maximise amount of drug exposure
Antibiotic	Penicillins	Aminoglycosides	Vancomycin
	Cephalosporins	Metronidazole	Colistin
	Carbapenems	(Fluoroquinolones)	(Fluoroquinolones)
	(Linezolid)		(Linezolid)
			Azithromycin

3.4.1 **Time-dependent** (see Figure 3)

Classes of antibiotics which exhibit optimal antimicrobial effect by time-dependency (also referred to as non-concentration dependent antibiotics) exert their effects by the length of duration the concentration exceeds the MIC over a 24h period. Further increasing the concentration above the MIC probably leads to better killing rates: current recommendations are that a drug exposure of ≥4-8x MIC could improve outcomes in patients treated with ß-lactam antibiotics. Antibiotic effect is ineffective if the concentration is below the MIC. The ß-lactams are typically time-dependent antimicrobials.

Previous recommendations suggested that optimal effects occur when the concentration of the antibiotic remains above the MIC for ≥40-75% of the dosing interval. However, current recommendations suggest that the t>MIC (for ß-lactams especially) should be as close to 100% of the



dosing interval to achieve optimal effects. This is particularly true in critically ill patients who, due to their altered physiology (see below), frequently fail to achieve desirable antibiotic concentrations. To achieve a prolonged period above the MIC, these drugs are sometimes administered as a continuous infusion (***AFTER A LOADING DOSE***), or as an extended infusion. Extended infusions are often used with imipenem and meropenem as they are not stable in solution for long time periods. Continuous / prolonged infusions with ß-lactam antibiotics seem to be of greatest value in critically ill patients, especially those infected with relatively resistant organisms (e.g. those with higher MICs).

Figure 3. Graph to illustrate time-dependent killing

3.4.2 Concentration dependent (See Figure 4)

Antimicrobials which work in this way rely on a high peak concentration (C_{max}) in relation to the MIC; this is how aminoglycosides act (although, in fact, aminoglycosides also fit into the AUC/MIC category as well and have some degree of time-dependence too…but their concentration-dependence is paramount!). For the aminoglycosides, it should be mandatory to measure a peak concentration 30 minutes after the infusion is completed. ***The peak level of aminoglycosides should be taken after the FIRST DOSE (I cannot emphasise this enough…..as there is this widespread, outdated belief that levels should only be taken on day 3….and it drives me NUTS and gives me grey hair – don't be that person!!!).*** Measuring a peak level after the first dose is crucial, as under-dosing is extremely common and you **MUST!!!!** give an adequate dose from the get-go. Under-dosing exposes the patient to the side-effects of a drug, without the effective therapeutic benefit. The best recommendation is to achieve a concentration of ≥10-12x above the MIC for that organism at the site of infection. Aminoglycosides are usually given as a once daily dose, yet they continue to have a clinical effect even when their concentration falls. This is due to their ***POST-ANTIBIOTIC EFFECT*** *(PAE)*, and is seen because the antibiotic is taken up into the organism and continues to exert its effects from within, even though the serum concentration has fallen. Metronidazole also demonstrates a PAE.

Trough levels should be taken on day 3, immediately before the dose is administered. ***T***rough levels relate to the ***T***oxicity of the aminoglycosides (ototoxicity, nephrotoxicity) since uptake of aminoglycosides by the inner ear and renal cortex is most marked at sustained levels. To minimise trough levels, the aminoglycosides are administered by ***extended interval dosing***, usually as a once daily dose.

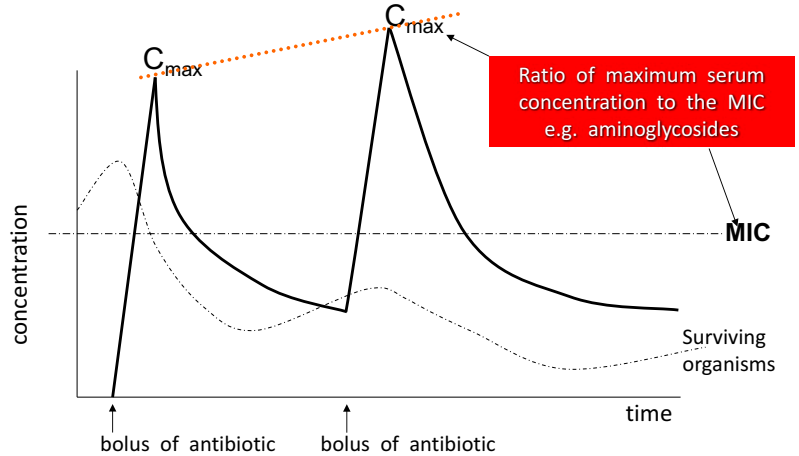


Figure 4. Graph to illustrate concentration-dependent killing

Some antibiotics demonstrate both time and concentration dependent killing. For Gram-positive cocci with an MIC <1µ/mL vancomycin demonstrates time dependent killing kinetics, but if the MIC >1µ/mL, it demonstrates concentration dependent killing.

3.4.3 A combination of concentration-dependent with time-dependency (See Figure 5)
Mathematically, this is expressed by the area subtended by the concentration-time curve and is expressed as $AUC_{0\text{-}24h}$/MIC. Specific values for the $AUC_{0\text{-}24h}$/MIC depend on the particular antimicrobial.

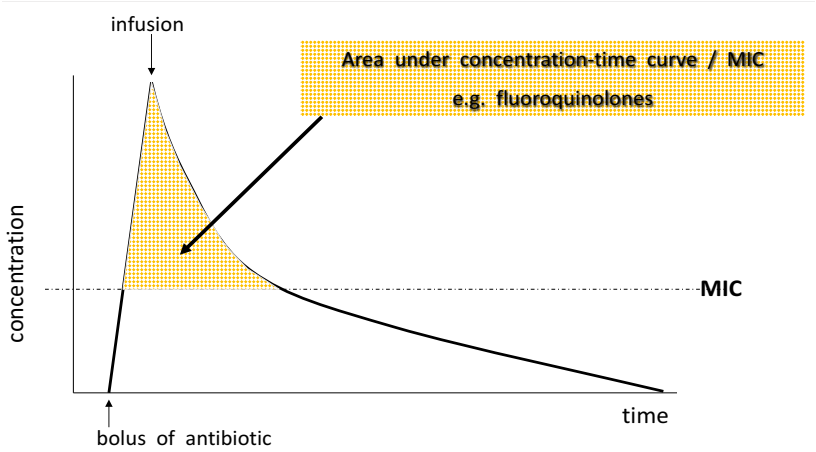


Figure 5. Graph to illustrate antimicrobial killing by $AUC_{0\text{-}24}$/MIC

4. Dosing

This is such an important area and we are cocking it up royally!!
The literature shows that we are under-dosing antimicrobials WAAAAAY more often than we are over-dosing. Sub-therapeutic dosing is a disaster as it leads to:

- Inefficient antimicrobial killing
- Compromised clinical outcome
- Non-lethal selection pressure which may cause:
  - The proliferation of multi-drug resistant organisms
  - Possible selection of hypermutable strains (which increases the mutation rate) and may result in acquired resistance to other antimicrobial agents
  - Increased movement of mobile genetic elements (like plasmids).

Most antimicrobials in clinical practice are hydrophilic (e.g. ß-lactams, aminoglycosides and glycopeptides). Lipophilic antibiotics include the fluoroquinolones and macrolides; from a dosing perspective, these compounds are easier to administer to septic patients as they tend to have intracellular accumulation and hepatic clearance, so only need their maintenance doses to be adjusted in the setting of severe hepatic dysfunction. Dosing of hydrophilic antibiotics may be tricky due to the increase in volume of distribution and renal clearance seen in septic patients. The increased volume of distribution and enhanced clearance results in sub-therapeutic concentrations of the hydrophilic antibiotics, which may compromise clinical outcome.

4.1 Increased volume of distribution (Vd)

Septic patients have circulating endotoxins and exotoxins which damage capillaries and cause capillary leak. This causes fluid to shift from the intravascular space to the interstitial space, taking with it hydrophilic molecules (importantly, antibiotics!!) which hugely increases their Vd and therefore reduces the serum concentration of the hydrophilic antimicrobials. In addition, vasodilatation and hypotension frequently require fluid resuscitation which, over hours, further expands the interstitium and further increases the Vd. It is important to recognise that the increase in Vd is only of relevance for hydrophilic antibiotics (the majority of antibiotics used in clinical practice), and not those which are lipophilic.

4.2 Increased renal clearance

The amount of hydrophilic antibiotic that remains behind in the intravascular space is also "under threat". Sepsis is frequently associated with a hyperdynamic cardiovascular system and an increased cardiac output, which in turn translates to an increased renal blood flow…and thus increased clearance of renally eliminated drugs. Antimicrobial clearance is proportional to creatinine clearance (see below in the section of augmented renal clearance).
In addition, septic patients are likely to have hypoalbuminaemia. Low albumin is associated with an increase in free fraction of the drug, although this may be advantageous initially, can lead to low concentrations later in the dosing interval. This occurs because the unbound form is a smaller molecule than the bound form, and is therefore more efficiently filtered by the kidney; thus, more antibiotic is eliminated in the urine. Hypoalbuminaemia is more clinically relevant when the antibiotics are both highly protein bound and predominantly cleared by glomerular filtration (such as ertapenem and ceftriaxone). Optimisation of dosing schedules in such scenarios should include the use of loading doses and higher-than-usual maintenance doses.

4.2.1 Augmented renal clearance (ARC) is a phenomenon that has only been recognised in the past decade, but is of great importance as it probably leads to faster elimination of drugs (including antibiotics), which in turn leads to sub-therapeutic concentrations and likely poor clinical outcomes (see Figure 6). ARC occurs when the urinary clearance of creatinine (CrCl) exceeds 130mL/min/1.73m^2 (normal values approximately 88-125 mL/min/1.73m^2 - with women having slightly lower levels than men). The exact mechanism remains unclear, but is, in part, related to: inflammation, increased renal blood flow, increased cardiac output, increased atrial natriuretic peptide and fluid resuscitation. ARC is estimated to occur in up to 65% of critically ill patients, and often occurs even in the setting of a normal serum creatinine. Young patients with polytrauma, burns, traumatic brain injury and lower severity of illness are particularly at risk of developing ARC. ARC is associated with sub-therapeutic antibiotic plasma concentrations of ***time-dependent antibiotics***, especially vancomycin and the ß-lactams. Recommendations are emerging that continuous infusions (or extended infusions) be used for these drugs, to maximise the duration of time that bacteria are exposed to adequate concentrations of antibiotics. Concentration-dependent antibiotics are **minimally affected** by ARC as their mode of action depends primarily on the peak concentration and volume of distribution, and not on the clearance of the drug.

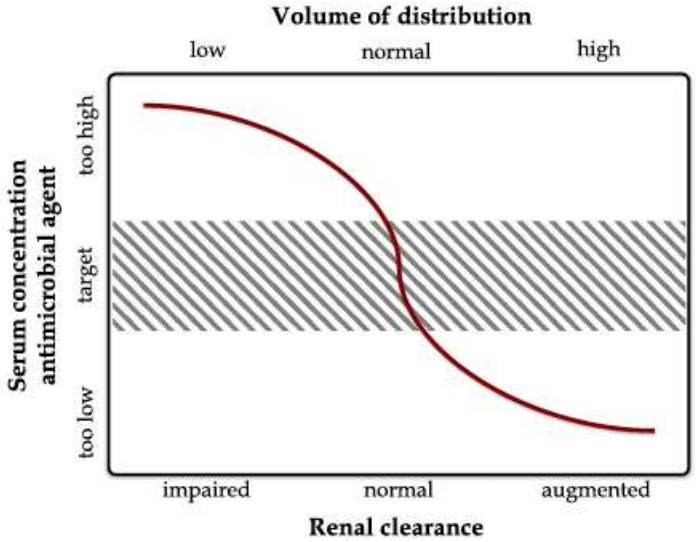


Figure 6. Graphical depiction of the effects of volume of distribution and renal function on serum concentration of hydrophilic antimicrobials.

4.3 Recommended doses

There has been an increase in the recommended doses of antimicrobials in the past few years. To summarise the above section: time-dependent and concentration-dependent antibiotics both require an increase in dose due to the increased volume of distribution seen in critically ill patients. In the setting of ARC, time-dependent antibiotics should be administered at higher doses (or continuous / prolonged infusions), whereas ARC does not have a big impact on concentration dependent

antimicrobials (which depend on the C_{max}/MIC). See Table 6 for recent recommendations of doses and dosing schedules

Table 6. Dosing schedule for some common antimicrobials

Drug	Recommended dose
Amikacin	25-30mg/kg daily **(N.B. not 1g!!!!!!)**
Cefepime	2g bolus and 6g daily over 24h
Ceftazidime	2g bolus and 6g over 24h
Cloxacillin	2g 6-hourly, or 3g 6-hourly in staphyloccal bacteraemia
Colistin	9-12mU loading dose then 3mU 8-hourly or 4.5mU 12-hourly
Ertapenem	1g 12 hourly
Gentamycin	7-9mg/kg daily **(N.B. not 320 or 400mg!!!!!)**
Imipenem	1g 6-8 hourly
Meropenem	1-2g 8 hourly
Piptazobactam	4.5g 6 hourly (or 4.5g bolus then 18g over the following 24h as a continuous infusion)

4.4 Dosing in acute kidney injury

Since many hydrophilic antibiotics are renally eliminated, a knee-jerk reaction is to automatically reduce the dose of (all) antimicrobials, including the first dose. The rationale behind this is that this will limit the toxicity from accumulation of the drug. This thought process is seriously flawed however, since the initial standard loading dose is likely to reach suboptimal serum concentrations due to the increased Vd (which initially is independent of renal function). Of course, with time, there will be accumulation of renally cleared (hydrophilic) antibiotics, but in the initial period this is not a concern. The literature does not have firm evidence as when to cut back on the standard doses of renally eliminated drugs, but recommendations are emerging to probably continue the usual doses for 24-72h before reducing the dose, to prevent accumulation and toxicity. However, there are a couple of important exceptions which need to be noted:

a) Drugs which are not eliminated by the kidneys are unlikely to pose such a problem
b) There may be compensatory elimination by alternative pathways. For example, ciprofloxacin is almost completely cleared by the kidneys, but in renal failure ciprofloxacin doesn't accumulate, as there is compensatory elimination by alternative pathways such as hepatic and trans-intestinal elimination.

Think twice before reducing the dose of antibiotic….there's a very good chance you may be ***WRONG***!!

4.5 What about in renal replacement therapy?

This is too detailed a topic to go into here, since the clearance of antimicrobial depends not only on factors such as Vd, plasma protein concentration and compensatory elimination, but also on the mode and dose of renal replacement therapy (RRT) as well as factors such as blood flow rate, dialysis filter material, and surface area. Although therapeutic drug monitoring may provide some clue, this is not widely available for all antibiotics and, in addition, only reflects plasma concentration and not necessarily effect site concentration.

4.6 Dosing in hepatic failure

Also not as straightforward as you might think!! Although the Child-Pugh score has previously been used to guide dosing, so far, the only antibiotics which need adjustment for Child-Pugh class C are metronidazole and tigecycline. Hepatic failure is associated with hypoproteinaemia, and thus an increase in unbound fraction of many drugs; however, it is estimated that a reduction in hepatic function by 90% is required before drug clearance is affected. In addition, hepatic blood flow is frequently increased in critically ill patients and this may compensate for the reduction in liver enzyme activity in drugs which have a high extraction ratio.

My advice: always go big. In septic patients, time is of the essence and achieving high effect site concentrations as soon as possible is paramount. The literature supports that we are under-dosing far more commonly than overdosing. Give big doses, as least for the first 48h...and probably for longer! However…there is a phenomenon called the Eagle effect, whereby when bacteria and fungi are exposed to high concentrations of antimicrobial (above the MIC, or minimum bactericidal concentration - MBC); paradoxically there is an improved bacterial survival and decreased rate of

bacterial cell death. Although this is fascinating and thought provoking, it's outside the required depth of knowledge for your examination! I should comment however, that MICs and MBCs are *in vitro* tests, and one cannot often be certain of the effect site concentration in clinical practice. Similarly, most of the examples of the Eagle effect have been demonstrated *in vitro* with only 2 case reports of it in humans (both in the setting of bacterial endocarditis).

5. Antimicrobial Stewardship

Few new antibiotics have been introduced into clinical practice in the past 10 years, and there is an urgent need to develop novel antibiotics since MDR organisms pose a growing threat to human life and health. Antimicrobial stewardship is ***crucial*** to our survival as human beings and boils down to "minimising antibiotic resistance whilst maximising antibiotic effectiveness". We must protect the antibiotics which we currently have by using them appropriately, to maintain their effectiveness. Overuse, misuse and under-use (such as occurs in under-dosing) all drive the emergence of multi-drug resistant organisms.

Prior exposure to antimicrobials places patients at an increased risk for developing an infection with a drug resistant organism; similarly, patients with the greatest exposure to antimicrobial are most often the ones who are infected with resistant organisms. Increasing antimicrobial resistance is associated with an increase in morbidity and mortality as fewer treatment options exist and the patient succumbs to their untreatable infection.

I'm not going to go into huge detail, despite the enormous importance of this section, but will give you a few bullet points and principles. www.fidssa.co.za is an excellent source for good articles on stewardship. The list below is modified from South African Antibiotic Stewardship Programme: A pocket guide to antibiotic prescribing for adults in South Africa 2015. Wasserman, Boyles and Mendelson).

- Is an antibiotic necessary?
    - About 50% of all antibiotic use is unnecessary
- Perform cultures before administering antibiotics
    - This helps to guide therapy after the initial empiric antibiotic choice, and makes de-escalation possible
- For empiric antibiotics:
    - Chose the antibiotic which targets the most likely pathogen at the site of infection
    - Consider the likelihood of antimicrobial resistance
    - Consider target site and adequacy of tissue penetration
    - Preferably use monotherapy with the appropriate spectrum of activity
- Ensure correct dose and route of administration
    - Dose according to the PK/PD principles which I have highlighted above
        - Give big doses!
        - Consider ARC (and organ dysfunction)
    - Aim for oral therapy except:
        - In certain infections such as meningitis, osteomyelitis, endocarditis and blood stream infections
        - In patients who are unable to swallow or absorb oral medication
        - In the setting of haemodynamic instability (this may be septic shock, but other shocked states also mean that absorption from the gastrointestinal tract or from intramuscular injections are unreliable)
        - For initial therapy for severe infections (always start with intravenous therapy in critically ill patients)
        - If no appropriate oral antibiotics are available
- Give early in severe infections
- Early and effective source control
- Evaluate appropriateness every day and avoid unnecessarily prolonged courses
- De-escalate as soon as possible. De-escalation includes the reduction in both spectrum nad duration of agents.

The WHO essential medicines list has divided antibiotics into 3 categories according to the **AW**a**R**e mnemonic to preserve the effectiveness of "last resort" antimicrobials (see Table 7). This is an attempt to ensure that the correct antibiotics are used for the right infection and to improve prescribing decisions. The categories are:

- **A**ccess – which antimicrobials should be widely available. These tend to be narrow spectrum agents which have a low risk of toxicity. Importantly, it is only from this group that prophylactic antibiotics should be selected.
- **W**atch – first or second line treatment for a small number of infections, or antibiotics which have a higher concern regarding toxicity.
- **R**eserve – which should only be used in severe circumstances as last-resort options and must be tailored to specific patients and clinical circumstances.

Table 7. List of *some of the* antibiotic classified into the AWaRe groups by the WHO

Access	**Watch**	**Reserve**
Benzylpenicillins, Phenoxymethylpenicillin	Antipseudomonal penicillins and ß-lactamase inhibitor (e.g. piptazobactam)	Aztreonam
Ampicillin	Carbapenems	4th generation cephalosporins
Amoxicillin	3rd generation cephalosporins	5th generation cephalosporins
Co-amoxyclav	Glycopeptides	Polymixins (e.g. colistin)
Cefalexin or cefazolin	Macrolides	Tigecycline
Cloxacillin	Quinolones and fluoroquinolones	Oxazolidinones (e.g. linezolid)
Doxycycline		
Gentamycin, Amikacin		
Metronidazole		

6. Mechanisms of antimicrobial associated harm

Infections caused by MDR pathogens are associated with an increase in morbidity, mortality and hospital length of stay. Aside from antibiotic use promoting bacterial resistance, antibiotics also have the potential to cause harm to patients through other mechanisms:

- Drug toxicity e.g. hepatotoxicity, nephrotoxicity, neurotoxicity, cytopaenias. Although the pathophysiology of toxicity is poorly understood, there is evidence that antimicrobials may affect human mitochondrial function and may contribute to organ failure in sepsis from bioenergetic failure.
- Adverse drug reactions which may be either dose dependent (predictable) and immunological (idiosyncratic).
- Dysbiosis. Pathogenic and commensal bacteria coexist in harmony in a microbiome; the use of antibiotics disrupts this balance and the resultant imbalance is termed dysbiosis. Alteration of the microbiome and dysbiosis increases the risk of infection, and the appearance of multidrug resistant organisms and may drive inflammation and organ dysfunction. Alteration in the microbiome and dysbiosis increases the risk of infection and contributes to the appearance of MDR organisms such as the ESKAPE organisms (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinteobacter baumanii,* and *Enteorbacter spp.*) which are responsible for many life-threatening infections in critically ill patients.

7. Closing remark

(I think) Antimicrobial therapy is perhaps the most important area of medical therapy, especially given the burden of sepsis and its associated high mortality rates. Unfortunately, it's an enormous area and I have limited space for these notes!! I hope that the notes provide some insight into some of the various intricacies of optimising antimicrobial therapy, and the damage we can do by getting this wrong!!

8. Glossary of terms

(that are often incorrectly used, and frequently interchangeable)!

Antibacterials act only on bacteria, this term encompasses all compounds that act against bacteria, including antibiotics.

Antimicrobials is a broader term that includes all agents that act against microorganisms, namely bacteria, fungi, viruses and protozoa.
Antibiotics are produced naturally by microorganisms and kill or inhibit the growth of other microorganisms, mainly bacteria. In purist terms, antibiotics do not include synthetic or semi-synthetic agents that are produced by chemical or biochemical synthesis, but for this lecture, they are all be lumped together under the term antibiotic!

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Notes

Iron Physiology
Key to understanding pre-operative anaemia correction

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Introduction

Anaemia affects one third of the world's population and iron is the cause in more than 50% of all anaemias[1]. Iron deficiency also affects up to 1 in 2 otherwise healthy women in South Africa, placing them at risk of anaemia, which has been associated with poor outcomes at childbirth and in the perioperative period. Beyond this, iron is now known to play a key role in every cell of the body, affecting things like mitochondrial energy metabolism in ATP production, storage of oxygen in muscles, function of cardiomyocytes, brain cells, the developing foetus, etc. This, together with the fact that patients can have almost all the symptoms of iron deficiency anaemia, even in the presence of a normal haemoglobin, has given rise to the concept of Non-Anaemic Iron Deficiency (NAID)[2]. Thus, for a human body to function optimally, iron deficiency should be corrected, whether the patient is anaemic or not. With anaemia being an independent predictor of poor outcome in surgery, optimising anaemia is now established as a key pillar of Patient Blood Management, which is a bundle of care, aimed at improving patient outcomes.

Iron Metabolism

Iron metabolism includes a number of steps, namely intake, absorption, transport, utilisation, recycling, storage and loss. Understanding how iron status and diagnostic testing can be affected at each one of these steps, is key to a clear understanding of the clinical features, diagnostics and treatment of iron deficiency.

Iron Deficiency Diagnosis and Treatment

Iron deficiency can be absolute where total body iron is depleted, but in many conditions, such as inflammation, cancer, infection, trauma, tissue damage, chronic renal failure, heart failure, etc., it may be challenging to diagnose iron deficiency, as the normal parameters to test for iron deficiency, may be affected by the underlying condition, and thus mask the diagnosis[3]. Understanding the basic physiology of iron deficiency can thus help greatly in distinguishing between simple iron deficiency and so-called iron restriction, both of which may require treatment with iron to correct anaemia[4]. Second, our current understanding of how iron is absorbed and recycled with changes in hepcidin and ferroportin levels, have a direct impact on the choice of treatment, e.g. oral versus intravenous iron. In this talk I will focus on how one uses serum iron, transferrin saturation, serum ferritin and some novel tests to help make a clear diagnosis and choose the right treatment from the start. In addition, we will look at novel ways of treating iron deficiency[5]

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Notes

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Blood and Blood Products
And a brief introduction to Patient Blood Management

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A brief history of blood transfusion

In 1628 William Harvey published the first description of the human circulation. This laid the foundation for the concept of blood transfusion. The first recorded animal study of successful blood transfusion occurred in England in 1665 when Physician Richard Lower kept dogs alive by transfusing blood from other dogs. This was followed shortly by transfusions from lambs to humans but resultant reactions resulted in a ban on further research. The first human to human blood transfusion therefore only occurred in 1795, performed by an American physician, Philip Physick.

Later, Dr James Blundell successfully transfused an obstetric patient in 1818 to treat postpartum haemorrhage. Using the patient's husband as a donor, he extracted approximately 110 ml of blood from the husband's arm and, using a syringe, successfully transfused the wife. Between 1825 and 1830, he performed 10 transfusions, five of which proved beneficial to his patients, and published these results.

Random fact alert: between 1873 – 1880 US physicians transfused milk (from cows, goats, and humans). Only in 1884 did saline infusion replace milk as a 'blood substitute' due to the increased frequency of adverse reactions to milk.

The discovery by Landsteiner of the four blood groups followed in 1901. In 1907 Hektoen suggested that cross-matching might improve the safety of transfusions. Reuben Ottenberg performed the first modern blood transfusions using typing and crossmatching in the same year.

Although the first blood donor service was established in 1920 by the British Red Cross, and the first blood bank in Leningrad in 1932, routine blood transfusion is a relatively recent medical phenomenon. In many ways, blood transfusion has been used as the standard treatment for perioperative anaemia. Blood is more readily available now and we transfuse more frequently, but there has been a shift in thinking with clearer understanding of both the positive and negative effects of blood product usage.

The application of evidence-based practices to optimise patient outcomes by managing and preserving the patient's own blood. Recently proposed as a potential solution for the South African context, Patient Blood Management (PBM) is particularly relevant considering the high prevalence of anaemia in our population, the severe blood product shortages, dwindling blood donor pool, and high demand for blood products.

Legal aspects

A balance must be reached between risk and benefit when choosing whether to transfuse a patient or not. This remains the prescribing doctor's responsibility. Objections to blood transfusions may arise for personal, medical, or religious reasons. For example, Jehovah's Witnesses object to blood transfusion primarily on religious grounds. If the patient's life could be saved by transfusion but the patient or their parents or legal guardians (in the case of a child) refuse transfusion, the courts may be called upon to intervene. There is a high court judge on call available to assist in difficult circumstances. Judges tend to rule in favour of transfusion.[1]

- The South African National Blood Service was established in 2001 when seven non-profit organisations amalgamated from across the country. Chapter 8 of the National Health Act requires the Minister of Health to issue a license to a non-profit organisation to deliver a nationwide transfusion service.
- The organisation is regulated by the minister of health and must comply with the regulations of the department of Health and the standards for the Practice of Blood Transfusion in South Africa.

Blood donation and blood procurement process

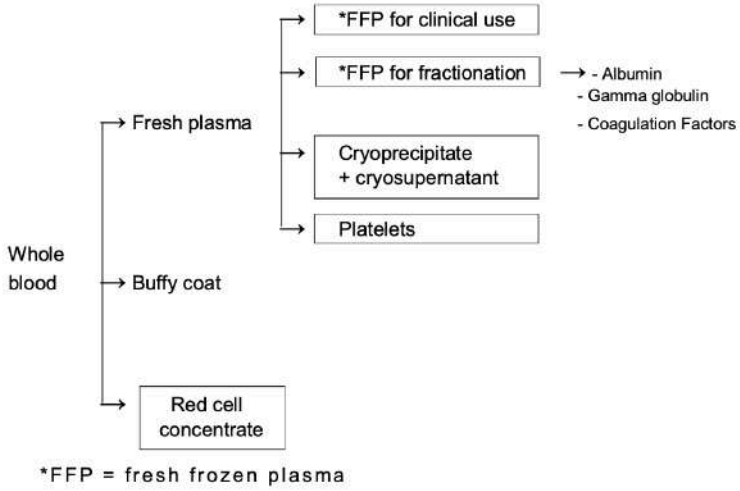
South Africa has a robust set blood transfusion rules and regulations (Standards of Practice for Blood transfusion in South Africa March 2016). Complex haemovigilance records are kept, with non-remunerated volunteer donors details maintained, strict quality controls and testing.

For their own protection, donors are required to comply with the following criteria:

- Age: Older than 16 years, and first time donors not older than 65 years.
- Weight: > 50kg (depending on the height of the donor)
- Haemoglobin: >12.5 g/dl
- Pulse rate of 50 - 100 beats per minute.
- Blood pressure between 100/60 and 180/100.
- Minimum donation interval of 8 weeks (12-16 weeks
- advised)
- Pregnant and lactating women are excluded because of high iron requirements.
- Exclusions of persons with:
    - Cardiovascular disease, including hypertension
    - Significant respiratory disorders
      - Epilepsy and other CNS disorders
      - Diabetes mellitus
      - Chronic renal disease
      - Ongoing medical investigations / clinical trials

Why single component therapy?

- One donated unit of whole blood can be used to make one unit of red cells, one quarter of an adult dose of pooled platelets, and either one unit of fresh frozen plasma (FFP) or one fifth of a dose of cryoprecipitate.
- **Advantages**: potentially useful products are not wasted by being transfused to those who do not need them.
    - Patients only receive the component they require, with less total exposure.
    - Aside from the added v**olume** of unnecessary components, significant complications of transfusion of red cells and platelets include the risk of:
        - Alloimmunisation (development of antibodies against red cell, leucocyte, and platelet antigens not possessed by the patient), which may cause adverse effects such as haemolytic and febrile transfusion reactions following subsequent transfusions.
    - Prevents a patient with chronic anaemia who requires repeated red cell transfusions from being exposed to unnecessary plasma with risks of transfusion related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO) and acute transfusion reactions.



Filters

- Red blood cells, whole blood, cryoprecipitate, FFP and Factor VIII concentrate are administered through a standard blood recipient set.
- 170 – 240 µm mesh filters: prevent the transfusion of clots or coagulation debris.
- Make sure the filter is covered with blood to ensure that the full filtering area is used.

- A platelet giving set should preferably be used with platelets although the standard filter administration set may also be used in an emergency.
    - However, this results in greater loss of the available platelets due to a larger surface area for adhesion.

The use of microaggregate (40 µm) filters is not recommended.

The administration set should be changed:
• When there is a transfusion reaction, in order to prevent further potentially harmful blood entering the patient's system
• Before infusing other fluids, e.g. Dextran, Ringers lactate

Be careful of adding other drugs or medications to a line being used for a blood transfusion as **bacterial contamination** is a real hazard whenever any unit of blood is entered. A reaction could also occur between drug and the anticoagulant or other fluid in the blood, e.g. Dextrose solutions might cause lysis or aggregation of the red cells in the transfusion set.

The only fluids that can be given **concurrently** through the same IV device as a red cell transfusion are:
• Normal saline • Calcium-free balanced salt solutions, e.g. Plasmalyte-L, Plasmalyte-B, Balsol, **modified** Ringer's lactate • 4% Albumin • Plasma protein fractions • ABO-compatible plasma

Blood products

Red cell compatibility

- Red cell transfusions **must be ABO compatible**.
- As far as possible, Red Blood Cell (RBC) transfusions should also be Rh-D compatible although, in an emergency, in situations of massive blood transfusion, or when there is a shortage of Rh-D negative blood, Rh-D positive blood may be transfused to Rh-D negative patients provided that the patient does not have pre-formed anti-Rh-D antibodies.
- Rh-D positive blood should also be avoided in females of childbearing age who are Rh-D negative. Antigen negative blood should always be transfused to patients with specific and clinically significant red cell antibodies.
- As far as possible, compatibility tests (a '**crossmatch**') should be performed **prior** to transfusion of red cells.

Storage of red cells

- Red cell products are preserved and stored at **1-6°C for up to 42 days**.
- During the storage of banked blood, changes occur which may be clinically significant.
- Donated blood is collected into a solution containing **sodium citrate**. Citrate is a stable, minimally toxic anticoagulant with pH buffering properties. Citrate is metabolized in the Krebs cycle of respiration and, after transfusion, is rapidly metabolized by most cells in the body, particularly in the liver, muscle and renal cortex.
- However, certain clinical conditions such as liver disease, hypothermia and hypoparathyroidism may place patients at risk for 'citrate toxicity' during **rapid** transfusion of whole blood or FFP. **Newborns** without adequate calcium stores, and with immature livers, are also at risk.
- Citrate may possibly contribute to cardiac arrhythmias and decreased cardiac contractility due to citrate's ability to lower plasma ionized calcium through chelation.
- The flow rate of citrate determines the degree of toxicity. A rate corresponding to 0.04 mmol/kg/min is associated with a significantly increased plasma citrate level and **a prolonged QT interval**.
- This may occur with massive, rapid transfusion of **whole blood** especially and, to a much lesser extent, RBC concentrates.
- If possible the ionised calcium levels should be monitored and 10 ml of 10% calcium gluconate administered intravenously (a rule of thumb is 10 ml for every 2 units whole blood given in under 10 minutes).
- Calcium and any other drug or solution **should never be directly added** to blood components.
- If calcium depletion is suspected, most modern blood gas analysers will give a very rapid measurement of ionised calcium.
- Any ionised calcium level **lower than 0.7 mmol/L**, should be treated. Calcium depletion alone is seldom a cause of impaired coagulation as the levels required to reduce coagulation are very low (<0.5 mmol/L).

2,3 Diphosphoglycerate (2,3 DPG)

- The concentration of erythrocyte 2,3 DPG **decreases** with storage.
- The function of 2,3 DPG is to facilitate oxygen transport.
- The binding of 2,3 DPG with deoxyhaemoglobin, and its interaction with oxyhaemoglobin, **shifts the oxygen-dissociation curve to the right**.
    - This reduces oxygen affinity of Hb and enhances oxygen delivery to tissues.
    - With significantly **decreased** 2,3 DPG levels, as occurs in **stored** blood after approximately one week of storage, the oxygen-dissociation curve is shifted to the left, **decreasing** oxygen delivery to tissues.

After transfusion, levels of 2,3 DPG are, however, regenerated in-vivo, with approximately 50% being regenerated within 7 hours, although full restoration of RBC 2,3 DPG can take up to 72 hours.

- In clinical situations of hypoxia and lactic acid production, and with decreasing pH, the oxygen dissociation curve is also shifted to the right, increasing oxygen delivery. Increased oxygen delivery also occurs with an increase in cardiac output.
- It is therefore generally considered that **low 2,3 DPG levels in stored blood are not usually clinically significant**.

Preservative solutions

RBC concentrates are prepared by the removal of most of the plasma, and the removal of the buffy coat layer (which is rich in leucocytes and platelets), from a unit of whole blood.

- A preservative solution (111 ml volume) is added to the residual red cells.
- This solution contains:
    - **adenine**: maintain ATP levels during storage
    - **glucose** (provides a substrate for RBC energy pathways)
    - **saline**
    - **mannitol**: reduces the haemolysis of the banked red cells during the 42-day storage period.
- Separating the buffy layer results in the **removal of approximately 70-80% of leukocytes** present in the original whole blood donation and significantly **decreases** the occurrence of non-haemolytic febrile transfusion reactions.
- The volume of a unit of red cell concentrate is approximately **300-350 ml** (including the additive solution) and the haematocrit is usually between **55% and 70%.**
- One unit of RBC concentrate (at a dose of **4 ml/kg**) can be expected to increase the Hb level of an average (70 kg) adult by approximately **1-2 g/dl**.
- Stored red cells experience loss of deformability and, on day 42 of storage, about 75% of red cells are viable.

Hyperglycaemia has been observed in certain clinical situations such as massive transfusion in orthotopic liver transplantation, or following cardiac surgery in infants, and has been attributed to the high glucose concentration in RBC concentrates stored in adenine additive solutions.

Electrolyte changes

At standard storage temperatures of 1-6ºC, the sodium-potassium pump is essentially **non-functional** and intracellular and extracellular levels gradually equilibrate.

- Plasma **potassium concentration increases** X8 over 28 days of storage although, at expiry, the total potassium load in red cell concentrates is only about 5.5 mmol/l.
- Therefore, the potassium load is rarely a clinical problem except in the setting of pre-existing hyperkalaemia. In these situations, fresh (<5 days) or washed red cell concentrates should

be used.

Plasticizer

- The plasticizer di (2-ethylhexyl) phthalate (DEHP) has been shown to leach from the plastic container into stored blood
- As storage time increases, the amount of DEHP detectable ranges from 6.8 to 36.5 µg/ml in RBC concentrates.
- The potential toxicity of transfused DEHP remains under investigation, but to date no studies have emerged indicating clinically significant effects.

Whole blood

Whole blood is a complex tissue from which clinically appropriate components are processed. Many of the components, particularly platelets and clotting factors, **deteriorate in whole blood** within hours of donation.

- It is therefore necessary to physically separate the components soon after donation so that they are available for use in the appropriate clinical situation.
- The clinical indications for using whole blood are limited since RBC concentrates are more appropriate in most situations where O2-carrying capacity needs

boosting.

- Indications:
    - Exchange transfusion in neonates
    - Massive haemorrhage

Packed Red Cells

RBC transfusion is a potentially life-saving treatment for blood loss and is the recommended therapy for restoring the diminished oxygen-carrying capacity in many circumstances.
The goals of RBC therapy:

1. to increase oxygen-carrying capacity of blood to meet tissue demand
2. to replace the oxygen-carrying elements of the intravascular volume lost during acute blood loss.

In patients who **do not have active bleeding** and in normovolaemic patients, the Hb should be measured **before and after** every unit of RCC transfused.

- Haemoglobin concentration is **dependent on both red cell mass and plasma volume** and it may fall due to haemodilution due to IV fluid administration.
- In the bleeding patient, **inadequate fluid resuscitation** may result in a **falsely elevated Hb** concentration despite significant blood loss.
- In the absence of blood products, or immediate need for blood products, the **initial** intravascular volume replacement strategies should mainly be **synthetic crystalloid and colloid** fluids.

Optimum Hb transfusion trigger

- Recent publications comparing more liberal transfusion strategies (typical transfusion trigger Hb 9–10 g/dL) with more restrictive strategies (typical transfusion trigger Hb 7–8 g/dL) do not show any difference in patient outcomes.
- **Therefore, a general Hb threshold of 7 g/dL should apply as a guide for red cell transfusion.**
- Uncertainty remains for patients with ischaemic heart disease, including ACS and after cardiac surgery and higher thresholds (8 g/dL) may be more appropriate in such circumstances (including patients going for major surgery and diminished oxygen reserve estimates).

Blood Components

FFP (Fresh Frozen Plasma)

- FFP is leucodepleted plasma rapidly frozen to below -25 °C to maintain the integrity of labile coagulation factors.
- The use of FFP has increased significantly in the past few years.
- Coagulation tests (PT or INR and aPTT) should preferably be obtained prior to the administration of FFP in a bleeding patient.
- Point-of-care whole blood viscoelastic testing is particularly useful in cardiac, liver, trauma and obstetric haemorrhage.
- Targeted blood component therapy based on Point-of-Care (POC)/visco-elastic testing has been shown to be safe and effective, and decreases blood product usage. There is no evidence however of improved outcomes.
- Transfusion of FFP is not indicated if PT, INR, and aPTT are normal (unless a patient has a condition such as thrombotic thrombocytopaenic purpura (TTP) or something like Factor XIII deficiency where both PT and aPTT may be normal).

Table 1: FFP contents

Factor	Average Levels
Fibrinogen	500 mg per unit of FFP
Factor II	1.03 IU/ml
Factor V	0.64 IU/ml
Factor VII	1.21 IU/ml
Factor VIII	0.85 IU/ml
Factor IX	0.95 IU/ml
Factor X	1.25 IU/ml
Factor XI	0.79 IU/ml
Antithrombin III	104 IU/ml
Plasma pseudo-cholinesterase	3 000-10 000 IU/ml

Table 2: Solutes

Factor	Average Levels
Glucose	24.8 mmol/L
Potassium	3.2 mmol/L
Sodium	165 mmol/L
Chloride	79 mmol/L
Osmolarity	322 mmol/L
pH	7.9

- FFP needs to be thawed before use.
- Once out of the fridge, it must be used within 30 min, and once thawed, it should never be refrozen.
- The approximate **volume** per bag is 300 ml.
- FFP contains **all the factors** of the soluble coagulation system, including the labile factors V and VIII to a varying degree.
- The **fibrinogen** content of four units of FFP is approximately 2 g, compared with approximately 4 g fibrinogen in two pools of cryoprecipitate.
- FFP should be the same group as the patient.
    - If the blood group is unknown, group AB FFP is preferred, as it does not contain any anti-A or anti-B.
- The recommended initial therapeutic **dose** is **10–15 ml/kg**.

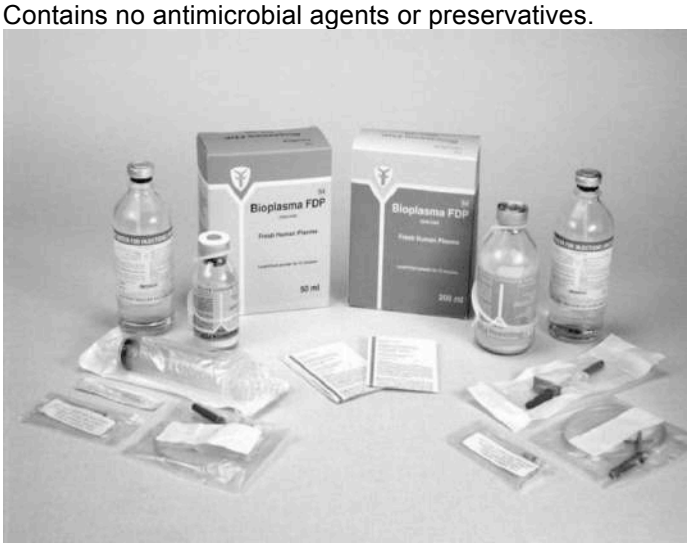
- **Indications** for FFP/FDP use include the following:

    - Maintenance of coagulation factors during **major haemorrhage**, particularly trauma and obstetrics.
    - **Acute DIC** with bleeding.
    - In patients who are **actively bleeding** and whose **INR is > 1.5** (or POC equivalent).
    - Immediate reversal of warfarin-induced haemorrhage when PCC is not available (PCC is the first choice).
    - Thrombotic thrombocytopenic purpura (preferably using pathogen-inactivated FFP or FDP)
    - Replacement of coagulation factors when specific factors are not available in the presence of active bleeding or to prevent bleeding during an invasive procedure (uncommon).
    - FFP/FDP is **not recommended** for routine use in patients with **cirrhosis/liver** disease unless significant coagulopathy and haemorrhage are identified.
    - **FFP should not be used simply as routine circulatory volume replacement.**

FDP (Freeze dried plasma) v FFP

First developed in the 1930s, pooled lyophilized plasma was widely used by British and American forces in World War 2 and Korean War. Initial concerns over hepatitis transmission have been alleviated by modern methods to improve blood safety. In South Africa, the National Bioproducts Institute has been producing Bioplasma FDP, a pooled, solvent/detergent, ABO-universal lyophilized plasma since 1996. Transfusion reactions are around 0.023%.

- Produced from pooled fresh human plasma
- It undergoes a pathogen inactivation procedure using a solvent detergent treatment process which inactivates lipoprotein-coated viruses including HIV, HBV and HCV.
- Pooled (up to 1,500 donors) - All volunteer donors
- After reconstitution with water for injection, each 100 ml contains 4-6 g plasma proteins
- Plus minimum of 0.4 IU/ml of each coagulation factor.
- **Indications**: whenever coagulation factors are required.
- Available either as a 50 ml or 200 ml pack size with water for injection and reconstitution set included.
- Contains no antimicrobial agents or preservatives.



- ABO-universal plasma
- Long shelf life
- Store below 25 °C
- Reconstitution: <10 minutes
- Where plasma and/or coagulation factors are required
- Contraindicated: Severe Protein S deficiency
- Hemovigilance program—no increase in adverse events

Platelets

Pooled Buffy Coat Platelet Concentrates

- Derived from the buffy coat layers of a whole blood donation separated within 8 hours of donation.
- The buffy coats from 4-5 donations are pooled and re-suspended in either plasma or a platelet additive solution (PAS).
- Following a gentle spin, the platelets separate from the other cells to yield a concentrated platelet suspension with a volume of 200-300 ml.
- The concentrate can then be filtered to produce a leucocyte depleted concentrate if indicated. Each unit contains a minimum of 2.4×10^{11} platelets.

Single Donor Apheresis Platelet Concentrates

- Collected from a **single donor** by a variety of apheresis systems.
- Current apheresis systems automatically **leucocyte deplete** the concentrate.
- Pooled platelet concentrates derived from whole blood donations and single donor apheresis concentrates have been shown to be **therapeutically equivalent** in terms of post transfusion increments and haemostatic efficacy, provided similar doses are given.
- There is **far greater donor exposure** with pooled concentrates; therefore patients requiring longer term support (e.g. haemopoietic **stem cell transplantation** and **chemotherapy** for haematological cancers) are preferably treated with single donor apheresis concentrates since the **risk of HLA allo-immunisation is reduced**.

- In bone marrow failure, therapeutic platelet transfusions are indicated in patients with **active, severe bleeding and thrombocytopenia**, although this usually occurs when the platelet count is **<10 x 10^9/l.**
- Patients with **chronic** sustained failure of platelet production (e.g myelodysplasia, aplastic anaemia) may not bleed abnormally despite platelet counts remaining consistently at <10 x 10^9/l. Prophylactic platelet transfusions are best avoided owing to the risk of allo-immunisation and platelets should only be given therapeutically to treat overt bleeding episodes.

Prophylaxis for Surgery

Lumbar puncture, epidural anaesthesia, gastroscopy and biopsy, insertion of indwelling lines, transbronchial biopsy, liver biopsy, laparotomy or similar procedures: **A threshold of 50 x 10^9/l is recommended.**

- **If patient is actively bleeding, transfuse to a platelet count > 50 x 10^9/L (> 75 x 109/L for neurosurgical and ophthalmic bleeding)**
- Surgery in **critical site**s (e.g. brain, eyes): Platelet count should be **>100 x 109/l**
- **Neuraxial blockade: 50 x 10^9/L**
- **If not bleeding, routine prophylactic use: 10 x 10^9/L**

Massive Transfusion

- Maintain platelet count at >50 x 109/l.

Disseminated Intravascular Coagulation (DIC)

- Maintain at 30-50 x 109/l. In chronic DIC or where there is no bleeding, platelet transfusions are not recommended just to correct a low platelet count.

Contraindications to platelet transfusions

- Autoimmune thrombocytopenia
- Thrombotic Thrombocytopenic Purpura (TTP)
- Heparin Induced Thrombocytopenia (HIT)

Cryoprecipitate

- The cold insoluble fraction of FFP
- Obtained by thawing FFP at 0-4°C
- Stored at or below -18°C for up to 1 year
- Available in volumes up to 15 ml
- Cryoprecipitate contains:
  - Factor VIII/vWF (approximately 100 IU per unit)
  - fibrinogen (150-200 mg per unit)
  - fibronectin and Factor XIII.
- Cryoprecipitate is indicated **primarily** for treating congenital or acquired **hypofibrinogenaemia** (defined as fibrinogen below the lower limit of the reference range for the laboratory) or dysfibrinogenaemia.
- Dose: 1 Unit Cryoprecipitate/10 kg body weight or 8-12 Units per adult dose.
- Given through a standard blood administration set.
- May also be used for treating hereditary Factor XIII deficiency.
- Recommended for both obstetric haemorrhage and massive transfusion

Haemsolvate Factor VIII

- This is an intermediate purity **Factor VIII concentrate** produced by NBI and prepared from pooled fresh human plasma.
- It is reconstituted into 10 ml volumes for direct intravenous injection
- Indicated for the treatment of **Haemophilia A** and **von Willebrand's Disease (vWD).**

Haemsolvex Factor IX

This is a **prothrombin complex concentrate** containing:

- prothrombin (factor II)
- factor VII
- factor X
- factor IX
- Reconstituted to a volume of 10 ml for direct intravenous injection.
- Indicated in the management of **haemophilia B** and the treatment of **warfarin induced bleeding**.

Plasma expanders

- **Albumin**:
  - Albusol 4% Human plasma albumin 4%
  - Albusol 20% Human plasma albumin 20%
    - Stabilised with 16 mmol/l acetyl tryptophanate and 16 mmol/l sodium caprylate. The solution: pH 7.0, < 100 mmol/l sodium, < 10 mmol/l potassium and <20 mmol/l citrate.
  - WCBS Albumin 20% S4 50 ml/100 ml
- **Protein Solution**
  - WCBS Stabilised Human Serum (SHS) 50/250ml
    - Stable protein solution containing IgG, IgA and IgM antibodies, albumin and transport proteins.
    - Available as a 5% solution (50 g/l protein) in 50 ml and 250 ml volumes
    - pH 7.5
    - Contains Na^+ 130 mmol/l sodium, Ca^+ 3.5 mmol/l and 130 mmol/l Cl^+

- From pooled human plasma from volunteer, non-remunerated donors
- Tested for HIV, HBV and HCV
- Albumin solutions are prepared by ethanol fractionation which further reduces the risk of
- viral transmission
- The albumin solutions are sterilised by filtration and finally pasteurised by heat for 10 hours at 60°C, a process validated to inactivate HIV, HBV and HCV
- SHS is prepared by selective absorption of lipoprotein, coagulation proteins and complement components
- Potential viral pathogens are reduced by this process and ultra-violet irradiation plus a heat treatment step validated as a viral inactivation procedure for HIV

Indications

- Replacement fluid following paracentesis:
- Therapeutic plasma exchange
- **Burns**: Often used after the first 24 hours in severe burns, but there is a lack of randomised clinical trials.
- Nephrotic Syndrome:
  - May have a short term limited role in combination with diuretics for the control of oedema, where diuretics alone have failed.
- Albumin solutions appear to have **no useful role** in malnutrition, cirrhosis and chronic nephrotic syndrome.

In Summary

SANBS/WCBS Blood products					
	Volume	Clotting factors	Fibrinogen levels	Dose	Cost in state sector (incl. VAT) March 2021
Whole Blood	513ml ± 45ml	Normal to decreased plasma levels (depending on length of storage)	Normal to decreased plasma levels	One unit	R 1 701,93
Red Cell Concentrate	300ml ± 50ml	None	None	One unit	R 1 532,78
FFP (Fresh Frozen Plasma)	280ml ± 70ml	Factor II Factor V Factor VII Factor VIII Factor IX Factor X Factor XI Antithrombin III Plasma pseudo-cholinesterase	500 mg per unit	10-15ml/kg	R 1 502,45

FDP (Freeze Dried Plasma) [Bioproducts institute]	50-200ml	100 ml contains 4-6 g plasma proteins + minimum 0.4 IU/ml of each coagulation factor	Equivalent to FFP	50-200ml initial dose	R 1141.49 /200ml
Cryoprecipitate	10ml ± 1ml/unit	Factor VIII/vWF (approximately 100 IU per unit), fibronectin and Factor XIII	150-200 mg per unit	1 unit/10 kg or 8-12 Units per adult dose	R 893,54/unit

Complications of Blood Transfusions

Non-infectious Serious Hazards of Transfusion

Acute
Acute haemolytic reaction
Allergic reaction
Anaphylactic reaction
Coagulation problems in massive transfusion
Febrile nonhemolytic reaction
Metabolic derangements
Mistransfusion (transfusion of the incorrect product to the incorrect recipient)
Septic or bacterial contamination
Transfusion-associated circulatory overload
Transfusion-related acute lung injury
Urticarial reaction

Infectious Complications of Blood Transfusions

COMPLICATION	*ESTIMATED RISK*
Hepatitis B virus	1 in 350,000
Hepatitis C virus	1 in 1.8 million
Human T-lymphotropic virus 1 or 2	1 in 2 million
Human immunodeficiency virus	1 in 2.3 million
Creutzfeldt-Jakob disease	Rare
Human herpesvirus 8	Rare
Malaria and babesiosis	Rare
Pandemic influenza	Rare

Random Donor Platelet Pool	> 200ml	Each unit contains a minimum of 2.4 x 10^{11} platelets	N/A	One pool = one adult dose Paeds: 5-10ml/kg	R 7 852,86

Major Haemorrhage

- Policies should be defined in an institutional major haemorrhage protocol.[2]
- Activation of the protocol should result in the immediate release and administration of blood components for initial resuscitation, without prior approval from a haematologist. Such protocols perform best when specific to clinical areas such as the emergency department or the labour ward, and are designed to include robust and clearly understood activation and communication from bedside to laboratory.
    - Their activation should also mobilise other resources, such as additional senior staff, porters, blood warmers, pressure infusers and cell salvage devices.

  - A clear mechanism for the escalation of a team response is necessary

- FDP can be substituted for FFP in the South African context.
- Group O RCC should be readily available and transfused if haemorrhage is life-threatening.
- POC/visco-elastic or laboratory testing should be used to guide management.
- During resuscitation, the following should be prevented/treated:
  - hypothermia
  - acidosis
  - hypocalcaemia (aim for ionised calcium > 1.0 mmol/L)
  - hyperkalaemia

- Most major haemorrhage packs will contain four units of RCCs and four units of FFP/FDP (equivalent to 15–20 ml/kg in a standard adult); platelet concentrate may also be provided.
- Administration should be via wide-bore IV access, or intra-osseous access until the former can be obtained.

Group O RBC should be readily available and transfused if haemorrhage is life-threatening and cross-matched red cells are not obtainable.

- It is preferable to give group O Rh-negative red cells to children and women of childbearing potential, but group O Rh-positive red cells may be used in adult men.

Group-specific RBC should be rapidly made available (within 15–20 min) by the laboratory after receiving a correctly labelled blood group sample and being informed of the emergency requirement for blood.

Haemostatic resuscitation

- This describes the process of restoring and sustaining acceptable tissue perfusion with the emphasis on preservation of effective clotting.
- Coagulopathy is associated with **haemorrhage (loss of platelets and clotting factors)** and transfusion of blood products and synthetic fluids (**dilution**), as well as the **mechanism** of injury in trauma; this may **exacerbate** the haemorrhage and resultant morbidity.
- Coagulation: POC/viscoelastic or laboratory testing should be used to guide management.

Paediatrics

There is little direct evidence to guide the use of blood products in children, and generally the guidance intended for adults can be safely applied to children with some modifications.
'Restrictive' approaches to transfusion are appropriate for almost all children older than 3 months of age.

- A transfusion of 10 ml/kg of RCC should increase Hb by approximately 2 g/dL.
- Cryoprecipitate should be given in a dose of 5–10 ml/kg. Platelets should be given in a dose of 10–20 ml/kg. FFP/FDP may be given in doses of 10–15 ml/kg.
- TXA can be used in children: a loading dose of 15 mg/kg followed by infusion 2 mg/kg/h should be used in trauma.[3]

Basics of Patient Blood Management

For more than 70 years the default therapy for anaemia and blood loss has mostly been transfusion. Accumulating evidence has demonstrated a significant dose-dependent relationship between transfusion and adverse outcomes. This and other transfusion-related challenges have led the way to a new paradigm. **Patient blood management** (PBM) is the application of **evidence-based practices** to optimise patient **outcomes** by **managing and preserving** the patient's own blood. [4,5]

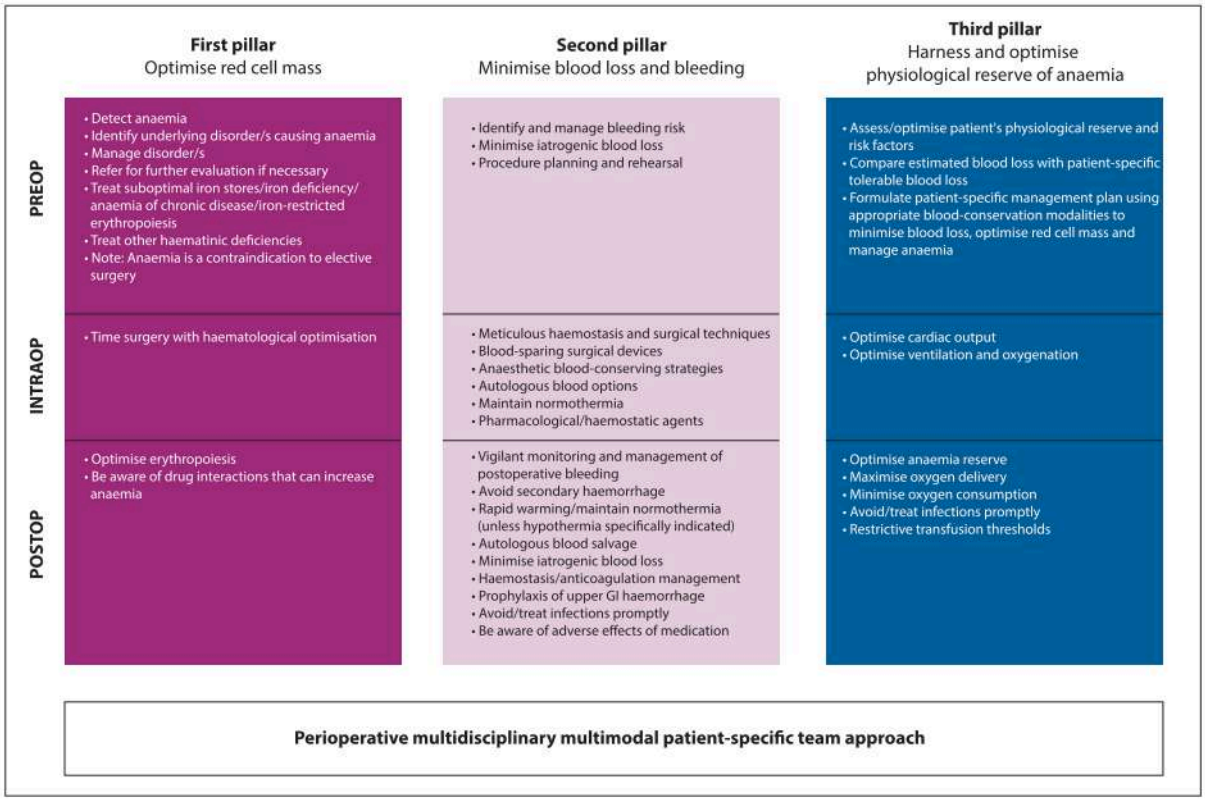
- 'Real-world' studies have shown that PBM improves patient outcomes and saves money.
- The prevalence of anaemia in adult South Africans is 31% in females and 17% in males.
- Improving the management of perioperative anaemia will
  - improve public health
  - relieve the pressure on the blood supply,
  - improve the productivity of the nation's workforce.
- While high-income countries are increasingly implementing PBM, many middle- and low-income countries are still trying to upscale their transfusion services

The aim is achieve these goals by the three pillars of patient blood management:

- optimising red cell mass

- minimising blood loss and bleeding
- harnessing or optimising the physiological reserves of anaemia while appropriate therapy is instituted
- This concept was adopted by the World Health Assembly resolution WHA63.12 in 2010

A similar and widely used description of PBM by the Society for the Advancement of Blood Management is 'the timely application of evidence-based medical and surgical concepts designed to maintain haemoglobin concentration, optimise haemostasis and minimise blood loss in an effort to improve patient outcome'.



A number of large observational PBM studies have demonstrated significantly improved patient outcomes including mortality, morbidity and average length of hospital stay.

The table above summaries the pillars of PBM and the various means to address these issues in the pre-, intra- and post-operative phases.[6]

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Notes

Introduction to Biostatistics
The Frequentist Approach

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Why statistics?

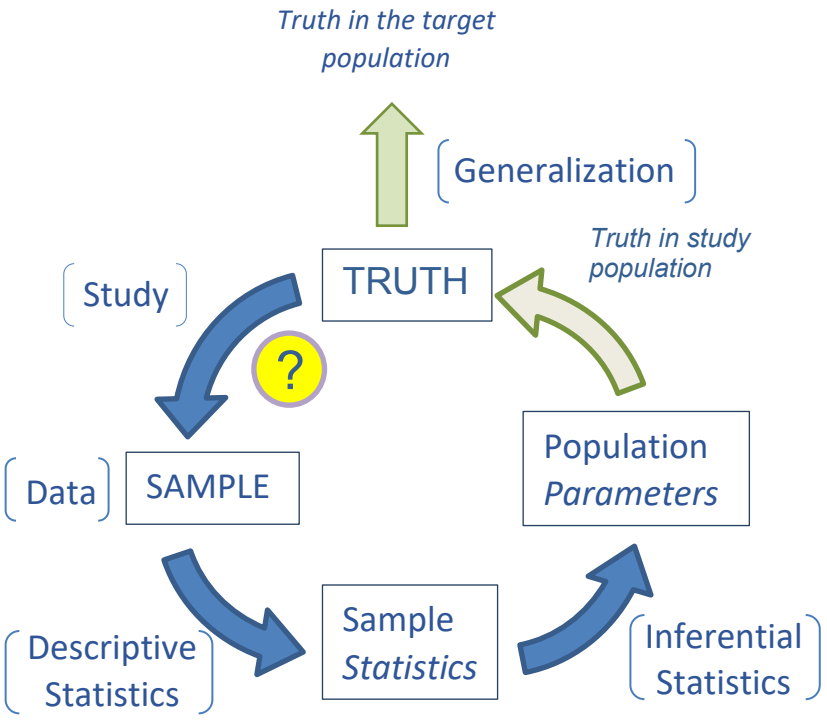


Figure 1: The research cycle

We conduct research because we are *uncertain* about the truth of a matter. Statistics in research is a box of quantitative tools we use to express our best *estimate* and level of *certainty* about some truth in question.

The research process starts with a specific research question. (E.g. *Compared to* balanced anaesthesia with Remifentanil, does opiate-free anaesthesia with Dexmedetomidine reduce in-hospital postoperative complications in noncardiac surgery patients?[1])

What are the PICO(T) components of a research question?

We design a study to address the research question. The best study design is determined by the research question, but typically the design we end up using is the one we can afford or have time for.

Which types of questions might we ask and how do they relate to study design?

[1] Note: The example research question refers to a real study. Beloeil H, Garot M, Lebuffe G, et al. Balanced Opioid-free Anesthesia with Dexmedetomidine versus Balanced Anesthesia with Remifentanil for Major or Intermediate Noncardiac Surgery - The Postoperative and Opioid-free Anesthesia (POFA) Randomized Clinical Trial. *Anesthesiology*. 2021 Apr 1;134(4):541-51.

In the conduct of our study we utilise measuring instruments to measure or count the variables that we are interested in. The instrument can be a physical laboratory instrument or a questionnaire or simply a defined method of counting an event of interest. The instruments generate observed data on our study sample.

While our question pertains to a broad target population we usually do not have access to the entire target population (both because of resource constraints and temporal constraints; we can only make observations in the present time). We are limited to a study population that we choose as representative of the target population. From this accessible study population we select a sample into our study. For our observations to be informative of our target population our sample must be *representative* of our study population and our study populations must be representative of our target population.

What is a census and what is the implication for inference?

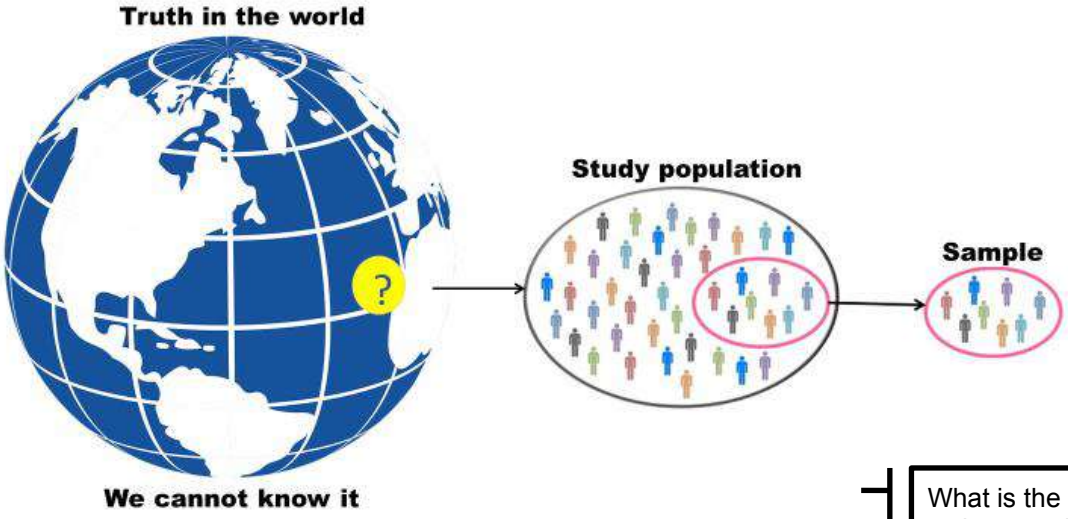
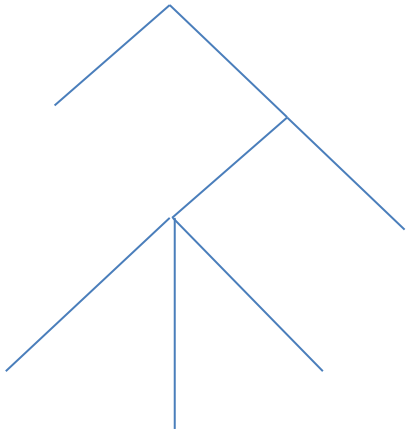


Figure 2: Representative sampling is key to external validity (generalizability)

What is the internal and external validity of a study?

Once we have our data, we use tools called descriptive statistics to generate *sample statistics* that describe our study sample. Next, we use inferential statistics to generate *population parameters* which represent our inference about the study population and by extension our target population.

Six Basic Study Designs



Design	Type	Temporality	Research Question
Ecological Study	Observational	Retrospective*	Occurrence & associations (at group level)
Case Study / Case Series	Observational	(Usually) Retrospective	Descriptive
Cross-Sectional Study	Observational	Snapshot*	Descriptive, Analytical, Diagnostic
Case-Control Study	Observational	Retrospective	Analytical (cannot describe occurrence)
Cohort Study	Observational	Prospective, but…	Descriptive & Analytical
Randomised Control Trial	Experimental	Prospective	Interventional & Analytical

***** Loss of temporal precedence. The exposure and outcome of interest is measured or recorded concurrently so that we can't tell from the data which came first – the chicken or the egg?

Study designs are either experimental (e.g. randomised control trials), in which participants are assigned to an exposure of interest, or observational, in which allocation to the exposure is not determined by the investigators. An analytical study compares participant groups against each other. The key difference between a cohort study, a cross-sectional study and a case-control study is the temporal nature of investigation. In the cohort study (a.k.a. a longitudinal study) participants are followed over time, allowing for the observation of exposure and subsequent outcome in a prospective manner. Note that, for the cohort study, the data collection does not have to occur prospectively, data can be collected completely retrospectively from a registry or partially retrospectively where exposure occurred in the past, but participants are followed prospectively to observe some outcome of interest that is yet to occur, regardless, we still think of the cohort study as following participants forward through time. The cross-sectional study observes the participant at one occasion only so that it is not possible to state from the data whether the exposure or the outcome occurred first. The case-control study selects case who have experienced some outcome of interest and then selects controls who arise from the same population as the cases but have not experienced the outcome. Next, the case-control study looks back into the history of the cases and the controls to measure some past exposure of interest.

The ecological study is a study that uses aggregate data instead of individual participant data to answer a research question. E.g. Looking at the relationship between Influenza vaccination coverage rates in different regions and comparing it to regional COVID-19 outbreak statistics when asking whether influenza vaccination protects an individual against COVID-19. The exposure and the outcome of interest are measured at a group level (aggregate data). The *ecological fallacy* refers to the false assignment of an association observed at the group level to the individual level. In this example an association between influenza vaccination coverage and the COVID-19 outbreak could be explained by differences in socioeconomic status between regions, so that aggregate differences in socioeconomic status create the illusion that influenza vaccination protects individuals against COVID-19.[2]

[2] Note: this is just an example – influenza vaccine may in fact protect against COVID-19. The jury is still out on this one. Amato M, Werba JP, Frigerio B, et al. Relationship between influenza vaccination coverage rate and COVID-19 outbreak: An Italian ecological study. *Vaccines*. 2020 Sep;8(3):535.

Types of quantitative data

Give an example of each data type for measurement of pain (5)

Numerical	Continuous*	Infinite potential data points between any two observations	Weight, Distance, Pressure, Current, Degrees, Time, and their derived variables
	Discrete	(Integers, Interval) Fixed known number of potential data points between any two observations	Counts. People, cells, objects
Categorical	Ordinal	(Ranked) The difference between consecutive data points is not quantifiable	Numerical clinical scores (Likert, GCS, ASA), ranked position, and categorization of numerical data
	Binary	(Dichotomous, Boolean) The observed variable has only two possible outcomes "yes-no" "true-false"	Death, Smoking, Pregnant
	Nominal	Qualitative groups that are not ordered	Ethnicity, Occupation, Gender

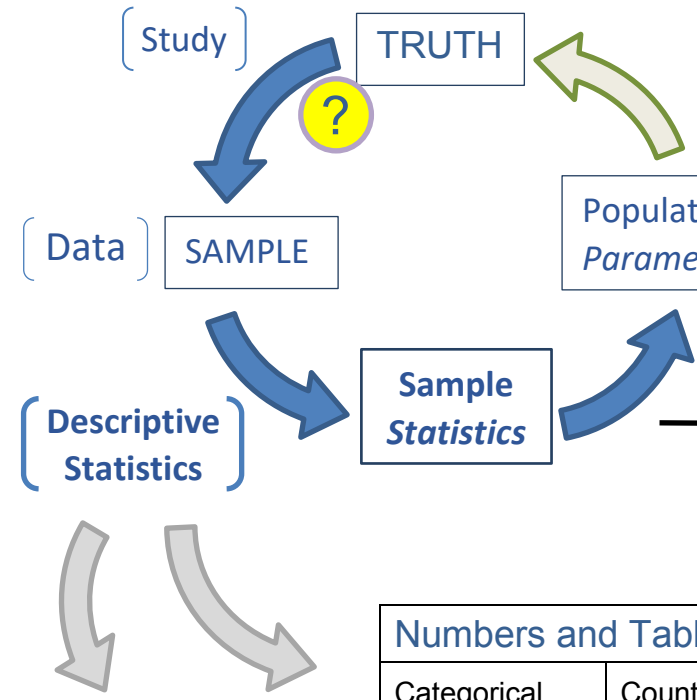
* Our measuring instruments can only measure discretely, however, the data is processed as that of the underlying data type. So even though our thermometer is only accurate to 0.1°C we still analyse it as continuous data, not discrete data. When we report the results, we stick to the level of accuracy of the measuring instrument.

Descriptive Statistics

We use descriptive statistics to summarise the observed data in our study sample. These summary values (mean, median, variance, etc) are referred to as sample *statistics* when we use them to describe our study sample. When we use these summary values to estimate some property of the population of interest (mean, median, variance, etc), the value is referred to as a population *parameter.* The appropriate statistics depend on the data type and data distribution. We also use data visualisation (plots ~ graphs ~ charts) to describe our observations.

$$\bar{x} = \frac{\sum x}{n} \qquad \mu = \frac{\sum x}{N}$$

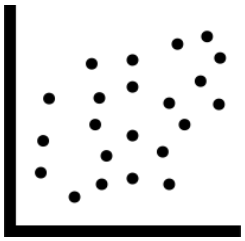
$$s = \sqrt{\frac{\sum (x - \bar{x})^2}{n - 1}} \qquad \sigma = \sqrt{\frac{\sum (x - \mu)^2}{N}}$$

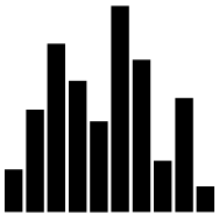


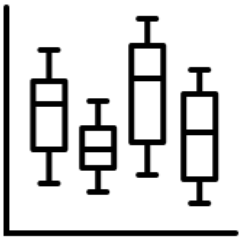
Distinguish between a sample *statistic* and a population *parameter*

Name the three data plots on the left side of the page and state which types of data each is used for

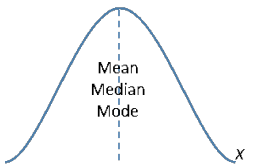
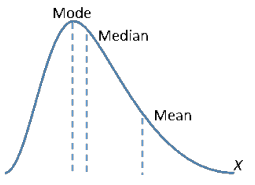
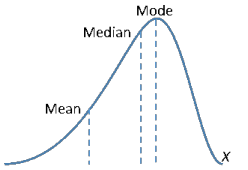
Descriptive Visualisation







Numbers and Tables		
Categorical Data	Count (n)	Proportion $(\%)$
Numerical	Central Tendency $(\bar{x},\ M)$	Dispersion (s, IQR)

Data Distribution		
Symmetrical	Mean = Median = Mode	
Positively / Right Skewed	Mean > Median > Mode	
Negatively / Left Skewed	Mean < Median < Mode	
Bimodal / Multimodal	≥ 2 Modes	

Inferential statistics

The process of estimating some parameter (mean, median, variance, etc) in the population from the observed study sample is called inference. We use point estimation (mean, median, variance) and range estimation (confidence intervals) for this purpose. Null hypothesis significance testing (p-values) is another frequentist method of inferring from the study sample to the study population.

The point estimate of the population parament (mean, median, variance, etc) is the same value as the sample statistic (mean, median, variance, etc), but while we were 100% certain of the sample statistic, we are uncertain of the population parameter because we did not measure everyone in the population. The level of uncertainty is expressed by the range estimate: the confidence interval. So we see that through sampling we gain efficiency (compared to a census), but we loose certainty.

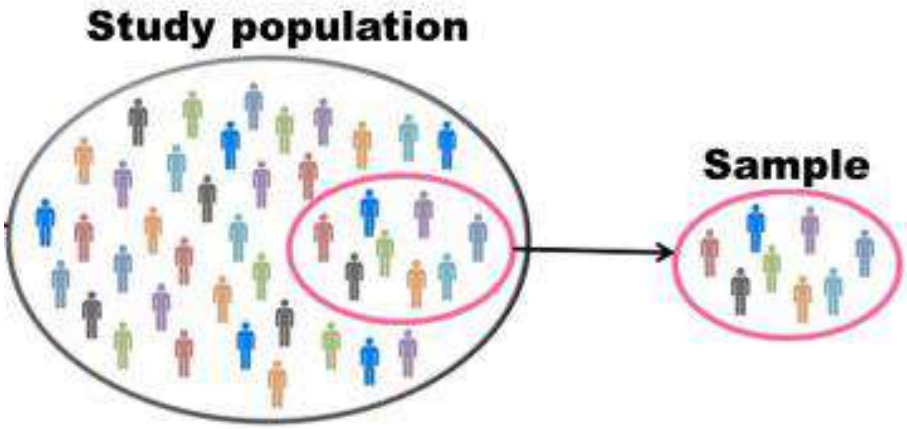
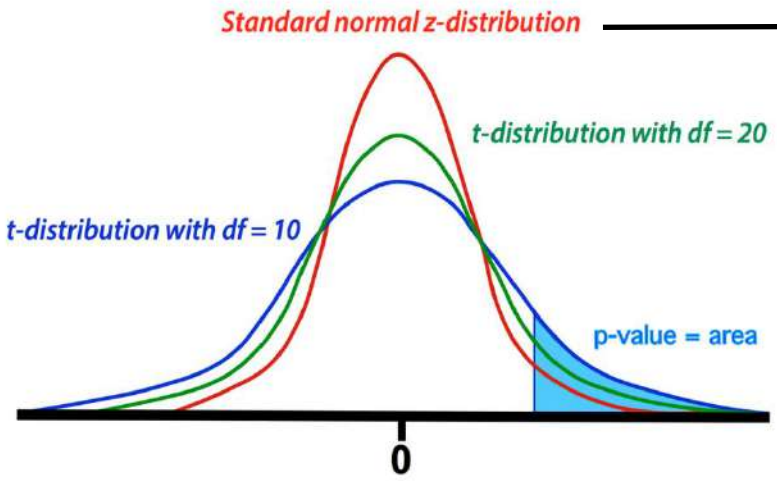


Figure 3: Probability sample

For the purpose of inference we have to assume that our study is made up of a true *probability sample* (Figure 3), that is, a *representative sample* of the population in which every person (or unit) had the same probability of being selected into the study. If we randomly sample *n* [number of] subjects from the same population repeatedly, the number of blue [trait or variable of interest] subjects in the sample will not be the same every time. If we sample 100 times and plot the proportion of study subjects with the blue trait in each of the 100 samples the plot will form a normal distribution (always) – regardless of the underlying distribution of the variable in the population. E.g. if we repeatedly estimate the average age of a population through sampling, the resulting histogram of age will have a normal distribution even though the underlying distribution of age in the population is not normal. This phenomenon is called the *Central Limit Theorem.* Figure 4.

In reality we only perform the study once, but we know that our sample statistic, which we use as the point estimate of the population parameter, represents some point on the normal distribution (z), more probably around the middle of the distribution and less probably at the extremes of the distribution. Because the normal distribution has known parameters, we can state a range within which the true population parameter lies with a specified level of certainly (confidence interval). The greater the number of subjects and the smaller the variation between subjects, the more certain we become of our estimate → narrower confidence intervals (smaller p-value). Figure 4.



While there are an infinite number of t-distributions there is only one standard normal (z) distribution and it has no degrees of freedom.

Figure 4: The sampling distribution of the population parameter (t)

The standard deviation of the sampling distribution is called the standard error (se), or the standard error of the mean (SEM) if the population parameter we are interested is the mean (but it doesn't have to be the mean). We can calculate the se from the values we observe in our study.

$$se = \frac{\sigma}{\sqrt{n}}$$

In practice we substitute s for σ

The standard deviation (s and σ) tells us how widely the observed data is scattered around the point estimate. The standard error (se) tells us about the precision of the point estimate. It will always be significantly smaller than the σ (if n > 1).

The terms precision, confidence interval and uncertainly refer to the same concept

Because our theoretical probability distribution (z) has known parameters we can use the se to calculate confidence intervals for our point estimate.

$$95\%\ CI = \bar{x}\ \pm 1.96 \cdot \frac{s}{\sqrt{n}}$$

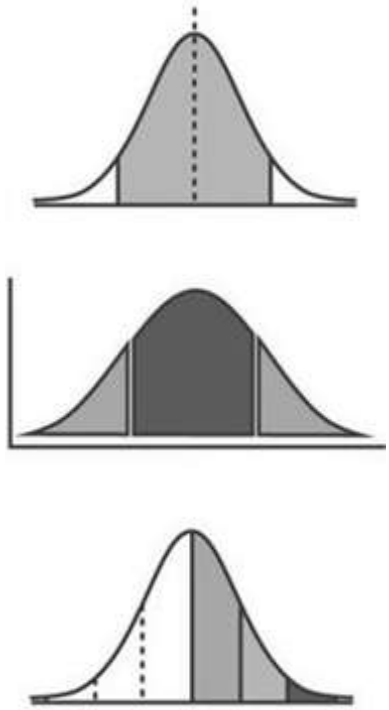
if $n < 30$ use the t-distribution with $df = n - 1$

$$95\%\ CI = \bar{x}\ \pm\ t_a \cdot \frac{s}{\sqrt{n}}$$

The 95% Confidence Interval is a range estimate for a population parameter. Practically it conveys the likely range of μ's (or whichever parameter is being estimated) that is consistent with the sample data. Theoretically, if we were to repeatedly sample the population, 95/100 times the $\bar{x}$ (or other sample statistic) will be included in this range, and by extension this range will also contain the true μ (or other population parameter).

The Normal distribution

There exist various theoretical probability distributions of which the parameters are defined, but the standard normal (z) distribution is our favourite. Other distributions that are commonly encountered are the t-distribution, the χ^2-distribution (chi-squared), and the F-distribution. Many of the null hypothesis significance tests rely on these distributions. We use these theoretical probability distributions to make inferences from our data to our population, they do not describe the distribution of our data.



Properties of the Standard Normal Distribution (Z)	
Derivation $(\mu = 0\,;\, \sigma = 1)$	$Z = \frac{x - \mu}{\sigma}$
Symmetrical	Mean = Median = Mode
Shape	Bell shaped
$\bar{x} \pm 1s$	68.3% of data points
$\bar{x} \pm 2s$	95.4% of data points
$\bar{x} \pm 3s$	99.7% of data points
$\bar{x} \pm 1.96s$	95% of data points

Null Hypothesis Significance Testing

Hypothesis testing is a form of inference that relies on our theoretical probability distributions.

	H_0 is TRUE $(\mu_1 - \mu_2 = 0)$	H_0 is FALSE $(\mu_1 - \mu_2 \neq 0)$
Reject H_0	Type I error (α)	True Positive
Fail to reject H_0	True Negative	Type II error (β)

What is the difference between the α and the p-value?

The level of significance in a study refers to α, it must be specified a priori. It is the probability of rejecting the null hypothesis when it is true. α is typically set at 5%, but this leads to a very high false positive result rate in published literature. Increasingly statisticians are calling for a smaller level of significance.

How does the p-value relate to the confidence interval?

The power of a study is the probability of correctly identifying a difference when it is there (i.e. rejecting the H0 when it is truly false). Power = 1-β. The p-value is derived by the chosen null hypothesis significance test and represents the probability of finding the difference seen in this study (or a greater difference) if, in truth, there is no difference in the population. It is the measure of extremeness of the results in light of the null hypothesis. It serves only as evidence against the H0 and cannot prove the H0 or any alternative hypotheses (specific or general). The p-value gives no information of the magnitude of effect (or difference), only the weight of evidence.

What is the difference between clinical and statistical significance?

Choose the correct hypothesis test for the data

		The Data	The Test
Numerical	Parametric	One sample	One-sample t-test of unknown variance
		Two samples with equal variances	Students two-sample t-test for independent variables
		Two samples with unequal variances	Satterthwaite's modification of the two-sample t-test (Welch's t-test)
		Paired samples	Paired t-test
		Correlation	Pearson's Correlation Coefficient
		≥ 2 samples with equal variances	One-way ANOVA with post-hoc pairwise comparison and Bonferroni's (or other) correction
	Non-parametric	Two samples	Wilcoxon Rank-Sum Test (Mann Whitney U test)
		Paired samples	Wilcoxon Signed Rank Test
		Correlation	Spearman's Rank Correlation Coefficient, or Kendall's Tau Coefficient
		≥ 2 samples with skewed data or unequal variances	Kruskal-Wallis Test with post-hoc Wilcoxon Rank-Sum comparison
Categorical	Single Proportion		95% confidence interval for single proportion (Z-test)
	Two Independent Proportions		Z-test comparing two proportions
	2 x 2 and larger *r x c* contingency tables of independent samples		Fisher's exact test always valid, χ2-test (chi-squared) only if expected values ≥ 5
	2 x 2 comparison of paired samples		McNemar's test for matched pairs; discordant pairs (b+c) ≥ 10
	2 x k comparison of binary outcome vs ordinal exposure		χ^2-test (chi-squared); n must be > 30
	Correlation between 2 categorical variables		Spearman's Rank Correlation Coefficient, or Kendall's Tau Coefficient

A parametric tests make assumptions based on the parameters of a specified theoretical probability distribution; e.g. the normal distribution. They are more powerful, but can be powerfully wrong when assumptions aren't met.

These above listed hypothesis tests only consider ≤ 2 variables (x or the relationship between y~x). When we want to consider the influence of additional variables, we need more complex tools. Regression analysis is the next step. The basic regression models are:

Data type	Regression method	Output
Continuous	Linear	Mean difference
Binary	Logistic	Odds Ratio
Count	Poisson; Negative Binomial	Incidence Rate Ratio
Survival	Cox Proportional Hazards	Hazard Ratio

Measures of effect

We should be primarily interested in magnitudes. These are expressed as various measures of effect. The measure of effect is determined by the data type and study design. For numerical data we express the magnitude of effect as a single mean (or median) or a mean difference (or median difference) or a standardised mean difference (SMD) between comparison groups. The magnitude of effect in categorical data is reported as occurrence and association.

Table: Measures of effect in categorical data

	Occurrence	**Relative Association**	**Absolute Association**
Cross-sectional study			
Measure	Prevalence (disease burden)	Prevalence Ratio	Prevalence Difference
Case-control study			
Measure	Odds	Odds Ratio (Cross Product)	*(Why is there no odds difference?)*
Cohort study (or RCT)			
Measure	Incidence (Proportion of Rate) = Risk; Incidence rate	Relative Risk = Risk Ratio, Relative Risk Reduction = Efficacy, Incidence Rate Ratio	Risk difference (Absolute risk reduction, NNT, Attributable fraction)
	Cumulative Hazard; Median survival	Hazard Ratio	Difference in cumulative hazard. Difference in median survival

The OR is used in all analytical designs. In the case-control study the interpretation is the odds of exposure in cases vs controls. In other designs the interpretation is the odds of an outcome in exposed vs unexposed. Mathematically these scenarios are equal.

Explain the difference between prevalent and incident cases

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Regina Nuzzo is a brilliant communicator. Her statistical discussions are accessible and insightful

https://journals.lww.com/anesthesia-analgesia published a fantastic statistical collection. These are some of the articles discussing basic statistical and research concepts.

Notes

The Oxygen Cascade

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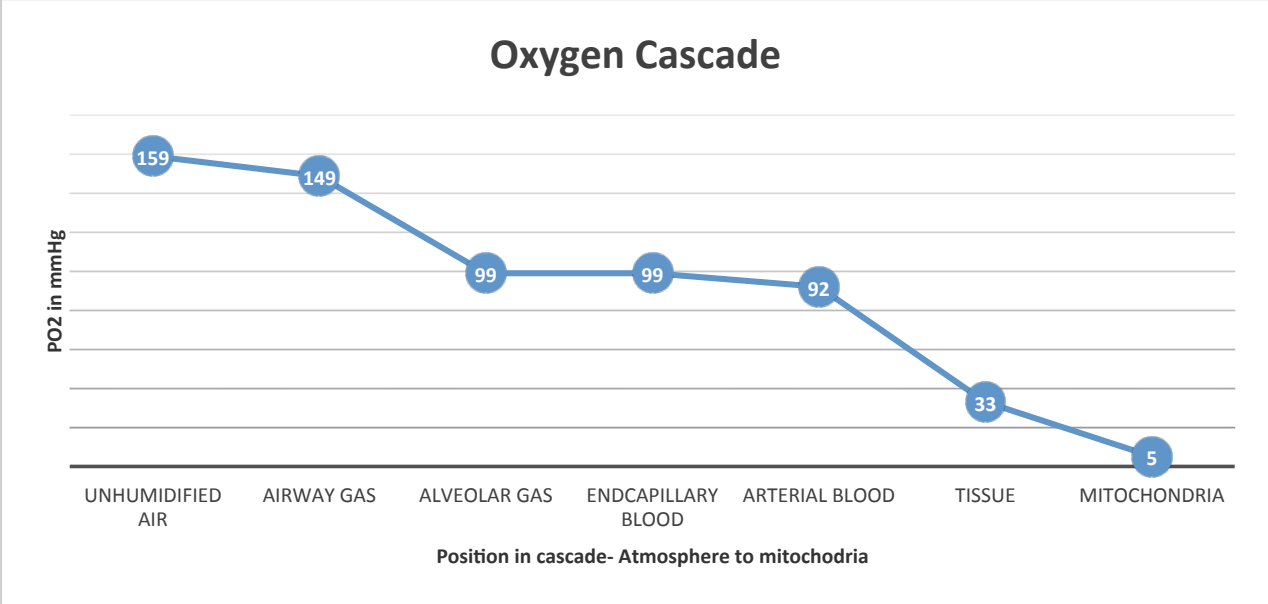
Oxygen is transported from the air that we breathe to supply each cell in the body. It moves from a high atmospheric pressure (concentration) to a low pressure (concentration) in the mitochodria. The movement of oxygen down this pressure gradient can be described by the oxygen cascade. The physiological reasons for the change in each concentration at different parts is described below. They can however also be caused by pathological reasons such as ventilation/perfusion mismatching, hypoventilation, diffusion abnormalities all of these can result in tissue hypoxia.



The highly aerobic human body consumes oxygen according to its metabolic demand.
The oxygen cascade is divided into different steps:

Step 1 and 2 of the process deals with optimizing the oxygen content.

Step 1: Transport from atmospheric air to the airway gas

- The oxygen needed for metabolic homeostasis is acquired from the atmospheric air. The partial pressure of the oxygen depends on Daltons Law and the Barometric Pressure (PB). Daltons Law states that the total pressure of a mixture of gases is equal to the sum of the partial pressures of the component gases:
  $P_{Total}=P_{gas\ 1}+P_{gas\ 2}+P_{gas\ 3}$
  Therefore

$$P_{O2\ atm} = 0.21 \times 760\ mmHg = 159mmHg$$

- This air is warmed to body temperature and humidified in the trachea-bronchial tree and nose. The partial pressure of oxygen is reduced due to the addition of water vapour. The pressure of water vapour is 47mmHg at a body temperature of 37°C.

$$Pi_{O2} = 0.21 \times (760-47) = 150\ mmHg\ (149.73)$$

This reduction is physiologically important when the reduction in barometric pressure becomes significant, such as on Mount Everest as seen in this graph:

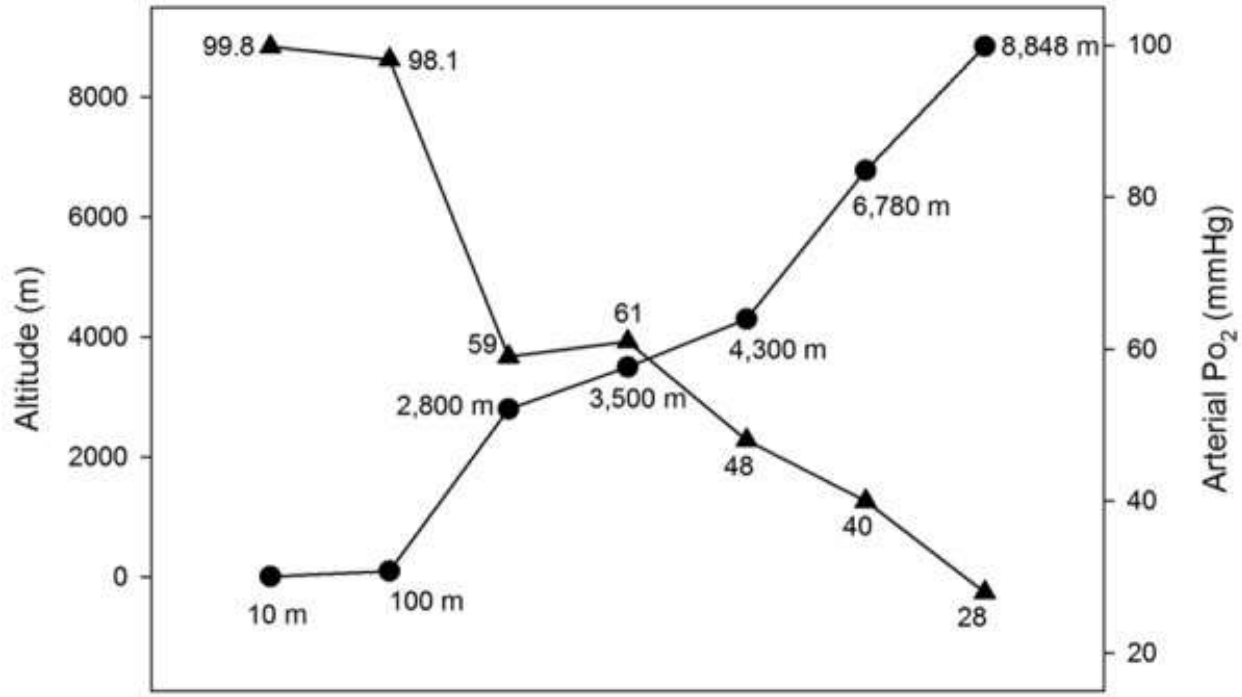


Fig 2: The influence of altitude in arterial oxygen content [1]

Step 2: Transfer from airway gas to the alveolar gas

Carbon dioxide (CO_2) is added to the PAO_2, effectively reducing the PAO_2 to 100mmHg. The $PiCO_2$ is almost certainly zero and the $PACO_2$ is normally around 40mmHg.
This is described by the alveolar gas equation:

$$PAO_2 = \{FiO_2 (PB - P_{H20})\} - \{1/R (PaCO_2)\}$$

PB Barometric Pressure
P_{H2O} Saturated water pressure at 37 °C
R Respiratory quotient normally 0.8 in a western diet (0.7 pure fat and 0.9 pure protein)

It is self explanatory that this is not possible for every alveolus, the alveoli in the alveolar dead space or those with a high V/Q ratio cannot be expected to contribute CO_2 to the same extent. Equally so there is the contribution of shunt- either due to under perfused alveoli or true anatomical right-left shunt- cumulatively referred to as the venous admixture. In both of these scenarios there is no exposure of the blood to the alveolar air. As long as the extent of these units is negligible, respiratory exchange can continue effectively. When there is a substantial V/Q mismatch this will result in hypoxia.

Step 3: Diffusion from the alveolus to the pulmonary capillary bed

The total transit time through the alveolar capillary is 0.75 sec. The entire process of oxygen transfer is normally completed in the first 0.25 sec.
Oxygen usually crosses the alveolar- capillary membrane without much difficulty.
There are 4 important factors for this to be efficient:

1. Large oxygen gradient
2. Large alveolar surface area with a thin membrane for diffusion
3. A diffusion coefficient that is favourable for oxygen
4. Oxygen hemoglobin dissociation curve that promotes rapid binding of hemoglobin.

Step 4: Transfer from pulmonary capillaries to systemic capillaries

The 7 mmHg difference between the end capillary blood (99mmHg) and the arterial blood (92mmHg) can mostly be explained by the addition of the venous admixture. Normal venous admixture is 3% of

cardiac output and shunt fraction 0.4-1 %

This is the amount of mixed venous blood that gets added to the ideal end capillary blood.

This can be explained by the following scenarios:

- Intrapulmonary shunt- Areas where the V/Q= 0 (blood travels through the lung without being oxygenated)
- Thebesian veins (smallest cardiac veins)- drain myocardial deoxygenated blood
- Bronchial veins- bronchial wall drainage
- V/Q scatter- areas where V/Q <1
- Intracardiac R to L shunts

Oxygen is carried in the blood in two forms either bound to hemoglobin or dissolved in the plasma and interstitial fluid. Oxygen has now diffused across the alveolar- capillary membrane and bound reversibly to hemoglobin. Hemoglobin occurs in two different forms *relaxed* (R) which has a high oxygen affinity and *taut* (T) which has a low oxygen affinity.

Bohr and Haldane effect

In combination these effects promote the release of carbon dioxide to the pulmonary capillaries and oxygen release to the tissue

The **Bohr** effect describes the relationship between hemoglobin's oxygen binding affinity (stickiness if we can call it that) and carbon dioxide and pH. Hemoglobin's affinity for oxygen decreases in an acidic hypercapnic environment, ensuring delivery of oxygen to the tissue.
B O-oxygen **H-** Hydrogen **R-** Released in the tissues

The **Haldane** effect describes deoxygenated hemoglobin's greater ability to carry CO_2 when compared to oxygenated hemoglobin.
H-Hemoglobin **A**-Affinity I **D**ane- Dioxide.

Hemoglobin can carry 1.34ml of oxygen per gram. If calculated fully saturated at a hemoglobin concentration of 15g.dl^{-1} , every litre can carry 200ml of oxygen. Only 3ml of oxygen will be dissolved. This dissolved oxygen obeys Henry's law.

The total arterial content of oxygen is calculated by the sum of the oxygen dissolved in the plasma and the oxygen bound to hemoglobin.

$$CaO_2 = (1.32 \times Hb \times SaO_2 \times 0.01) + (0.0225 \times P_aO_2)$$

CaO_2	Arterial content of blood
1.31	Hufner constant (directly measured maximum oxygen carrying capacity)
SaO_2	Percentage of saturated hemoglobin
0.0225	Oxygen solubility coefficient.

Step 5: Diffusion of oxygen from the capillaries to the cell

$$\text{Delivery of oxygen} = Q \text{ (Cardiac output)} \times CaO_2 \text{ (arterial content of oxygen)}$$

In order to determine the oxygen consumption in a particular vascular bed we can calculate the difference between the arterial and venous content. For example if we were to sample the left renal artery and vein the difference would represent the oxygen uptake.

Therefore, if you were to estimate the whole body oxygen consumption over time you could sample the proximal aorta and proximal pulmonary artery and measure the PvO_2 and the PaO_2.

Now knowing that the difference between PaO_2 and PvO_2 equals the oxygen consumption in any given organ we can calculate it as follow:

$$CaO_2 = (1.32 \times Hb \times SaO_2 \times 0.01) + (0.0225 \times P_aO_2)$$

$$CvO_2 = (1.32 \times Hb \times SvO_2 \times 0.01) + (0.0225 \times P_vO_2)$$

And the oxygen consumption VO_2

$$VO_2 \text{ ml } O_2/\text{min} = (CaO_2 - CvO_2) \times Q$$

Factors that determine the oxygen consumption of specific tissue depend on the cellular oxygen demand.

Increase VO_2	Decrease in VO_2
Pain Shivering Exercise Trauma Inflammation/sepsis Pyrexia Agitation	Sedation Analgesia Neuromuscular blockers Mechanical ventilation Hypothermia

Oxygen extraction ratio is the fraction of oxygen delivered to the tissue that is utilized by the tissue, it is the ratio of consumption: delivery. Normally 20-30% of delivered oxygen is utilized. This can be calculated if we use the figures from a normal healthy adult.
Namely VO_2 254ml/ min^{-1} and DO_2 998 ml/ min^{-1}

$$O_2ER = VO_2 / DO_2$$

From the aorta the oxygen released from the hemoglobin depends upon the specific metabolic demand of that organ. This is usually matched to the arterial supply and vasomotor sensitivity of the specific organ.

Therefore at this stage of the cascade it is difficult to give a specific value of the PaO_2 as it is highly dependent on the organ.[1]

Tabel 2: Partial pressure of oxygen in different organs[1-4]	
Organ and tissue	*$Pt0_2$*
Brain	30-48
Alveolus	104-108
Small Bowel	61
Umbilical artery	18
Umbilical vein	29
Liver	55
Cortex of the kidney	70

Step 6: Diffusion to the mitochondria

In the inner membrane of mitochondria has five sequential enzyme complexes referred to as the respiratory chain. 4 of the 5 complexes ensures reduced nicotinamide adenine dinucleotide (NAD) + hydrogen (H) to the fifth, ATP synthase. Oxygen is utilized to generate CO_2 and H_2O. The incompletely oxidized molecules turn into reactive oxygen species (ROS) which is normally cleared by antioxidant mechanisms and therefore detoxifies it. The oxygen partial pressure in the mitochondria is normally 1-10mmHg.

Oxygen storage

Despite our dependence on oxygen our oxygen storage ability is very small and we would not be unable to sustain life beyond a few minutes. The oxygen content of the blood depends on the concentration of hemoglobin and blood volume. The oxygen content in the lungs depends on the functional residual capacity. Breathing room air, both these stores (lung and blood) are small. When breathing 100 % oxygen this causes a major increase in oxygen storage as the entire FRC is filled. Now the major store is the lung, up to 80% of this oxygen can be utilized before there would be any significant drop in hemoglobin saturation. Explaining the rationale for pre-oxygenating your patient.

Pathological states that cause hypoxia

Anemic Hypoxia

This occurs when the oxygen carrying capacity of blood declines. By implication there are fewer hemoglobin molecules available for binding.

Multiple causes can exit, here are a few:

- Decreased hematocrit (hemorrhage/ immune mediated hemolytic anemia)
- Carbon Monoxide poisoning- irreversible combination of CO with hemoglobin and also shifting of the OHDC to the left
- Methemoglobin- conversion of heme-binding sites to methemoglobin and thus rendering it impossible to bind oxygen (can occur with nitrate)

Stagnant or Hypoperfusion Hypoxia

As the name implies this occurs due to low flow state. Decreased blood flow causes the primary limitation in the delivery of oxygen. This problem therefore is mainly in the cardiovascular system, centrally (reduced cardiac output-pump failure) and peripherally (ischemic perfusion). In an attempt to continue to meet the demand the amount of oxygen extracted increases and this would then lead to a decrease in PvO_2. Interventions to improve the cardiac output or peripheral tissue perfusion will help in this situation

Causes:

- Anaphylaxis
- Systolic cardiac failure – such as ischemic or dilated cardiomyopathy
- Massive pulmonary embolism
- Hypovolemic shock
- Anaphylaxis

Hypoxic Hypoxia

If the PaO_2 falls, we refer to it as hypoxic hypoxia. In this case the primary problem is in the respiratory system.

There are many causes for this:

- Fall in the inspired oxygen concentration (such as rise in altitude)
- Primary respiratory problem (hypoventilation, V/Q mismatch, diffusion impairment, anatomic shunt)

Due to the decrease in oxygen transportation the circulatory system attempts to improve this in two ways:

Capillary vasodilation in order to increase the surface area and decrease the diffusion distance- this improves the area for oxygen exchange. Secondly arterioles dilate to increase perfusion and therefore delivery. Treatment depends on the specific cause but increasing the inspired oxygen will cause improvement in most instances except if there is a pulmonary shunt.

Histotoxic Hypoxia

This refers to reduction in adenosine triphosphate (ATP production) in the mitochondria. There is therefore a defect in cellular utilization of oxygen. The best example of this is cyanide poisoning. The cause of the profound cellular hypoxia is due to the impasse of the reaction of oxygen with cytochrome c oxidase by cyanide. Treatment of cyanide poisoning is with the cyanide antidote combination kit that contains amyl nitrite, sodium nitrate and sodium thiosulfate. These nitrates form methemoglobin which causes binding of cyanide.

Table 3: Variable Changes utilizing Fick's Principle to analyze hypoxia[6]				
Cause of Hypoxia	***PaO_2***	***PvO_2***	***CO***	***VO_2***
Anemic	N	↓	N or ↑	N
Hypoxic	↓↓	↓	↑	N
Stagnant	N	↓	↓↓	N
Histotoxic	N	↑	N	↓↓

Pasteur Point

What is the lowest oxygen tension that the mitochondria can tolerate before trying to utilize it as energy source? The critical threshold of oxygen is described by many authors as some sort of "Pasteur Point". This term is adapted from microbiology and eludes to the oxygen tension required for a anaerobic organism to switch their metabolism from anaerobic fermentation to aerobic. Below this critical level the microorganism views the oxygen tension an unfeasible means of energy generation. For mammals this critical threshold is probably around 7mmol/L (0.5mmHg).

Conclusion

The transport of oxygen from the air to the tissue is clearly complex and each step of the cascade is affected by multiple factors. Though understanding these fundamentals of how the respiratory and cardiovascular systems combine to facilitate the transport of oxygen to its ultimate utilization in the mitochondria is important in understanding how we approach and treat the pathological processes at different levels.

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Notes

Anti-arrhythmic Agents

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The heart is little more than a group of complex electrical circuits which are bathed in, and suffused with, an electrolyte solution. The power supply for the circuit is built-in and receives charge from millions of constantly running ion pumps which maintain both the standing electrical potential across membranes and the oscillating currents which result in depolarization and repolarization. These pumps receive energy from ATP which is supplied chiefly by the oxidation of fatty acids by the mitochondria.

The point is…

Disruptions in cardiac rhythm arise just as short circuits arise in any piece of electronic equipment:

- By physical disruption of the architecture
    - Cardiac anatomical abnormality
        - Congenital or acquired.
- By alteration of the environment the circuit is situated in
    - Electrolyte solution abnormality
        - Hyper/hypo
- By disruption of the circuit power source
    - Fuel supply disruption
        - Lack of metabolic fuel
        - Lack of oxidizing agent

The focus of any antiarrhythmic prescription needs to be restoring conditions suitable for the normal functioning of the circuitry. Antiarrhythmic medications are diverse in their effects on the functioning of the circuit and a targeted approach is necessary to maximize success.

As corrections of cardiac fuel supply and anatomical abnormality are likely dealt with elsewhere in the curriculum, this note will concern itself largely with electrolyte abnormality and therapies aimed at manipulating ion currents.

Before moving on it is worth stating that it is largely fruitless to focus on correcting the electrolyte environment of the heart when the cause of the arrhythmia in question is related to an anatomical disorder or a fuel imbalance. Failure to correct these while focusing on the information contained below is likely to yield disappointing results.

Classification of antiarrhythmic agents

A detailed description of all the possible classification methods for antiarrhythmic medications is beyond the scope of this note set. The most commonly studied system for the FCA exams is the Vaughan Williams classification which attempts to group these medications according to their predominant site of action. This approach, although simple and easy to remember, has some disadvantages:

- Several of the medications have more than one site of action and the combination of these actions is more important than any one of them alone
- The schema has no allowance for several commonly used drugs
- Drugs in the same group often have different effects

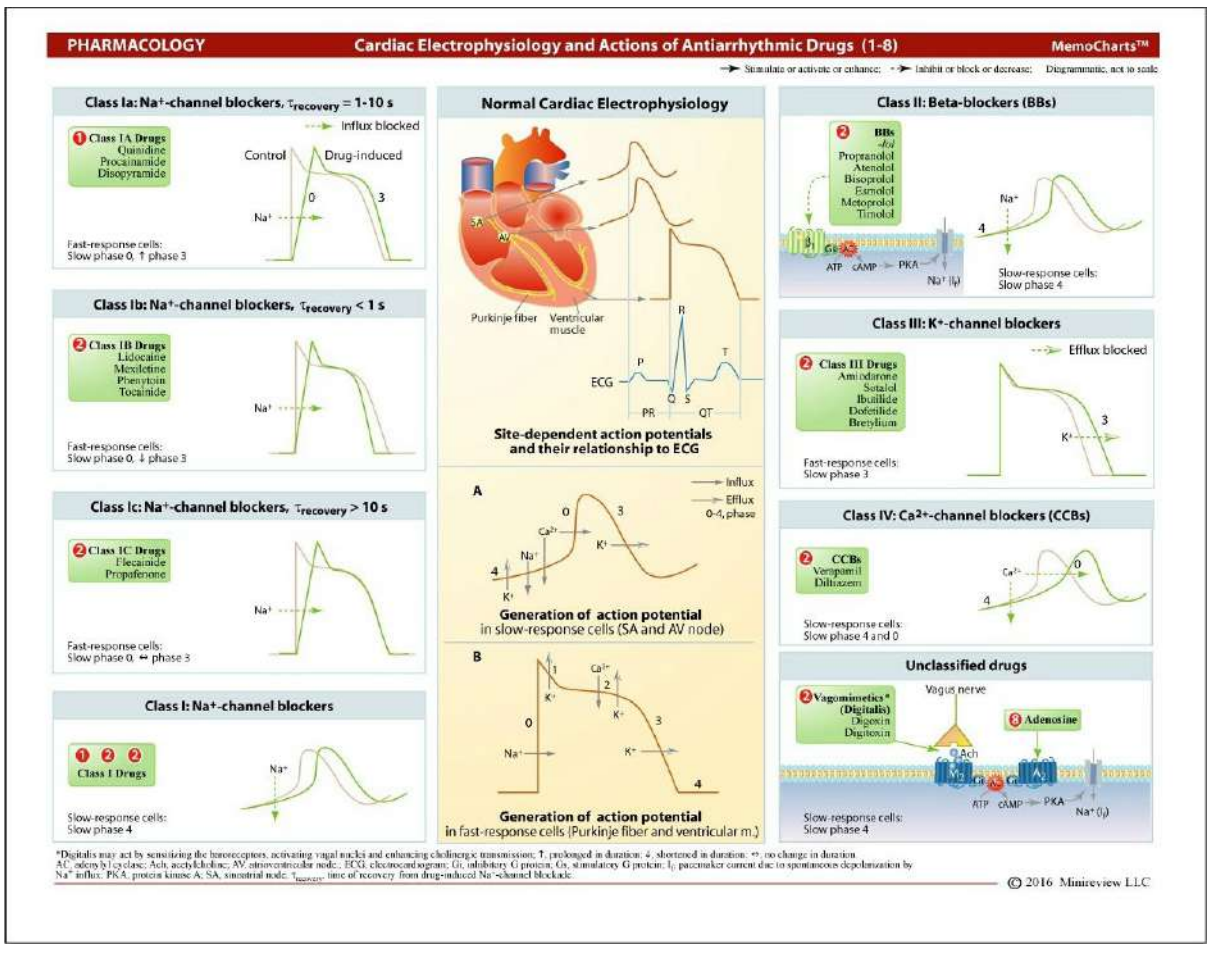
Regardless, for the purposes of this discussion, the classification is provided in the diagram below.

Drug	Channels					Receptors				Vaughan Williams Class
	Na			Ca	K	α	β	M_2	P	
	Fast	Med	Slow							
Lidocaine	●									Ib
Procainamide		A			●					Ia
Disopyramide		A			●			●		
Quinidine		A			●	●		●		
Propafenone		A					●			Ic
Flecainide			A		●					
Verapamil	●			●		●				IV
Diltiazem				●						
Bretylium					●	●	●			III
Sotalol					●		●			
Amiodarone		●		●	●	●	●			
Propranolol	●						●			II
Atropine								●		
Adenosine									●	
Digoxin*								●		

Relative blocking potency:
● Low
● Moderate
● High

● Agonist
● Agonist/Antagonist

A=Activated state blocker
*Digoxin is also a Na/K ATPase pump blocker (high relative potency)



The final panel notes important antiarrhythmics are not included in the above classification namely adenosine and digoxin, their pharmacology will be dealt with later.

The Vaughan Williams classification is not the only valuable system to know. Below is a modification of another classification system called the Sicilian Gambit. It is useful as it includes details of more than one of the ion channel effects for each drug as well as some of the cardiac and extra-cardiac effects. It is useful for distinguishing between drugs in the same Vaughan Williams class.

Key Points to remember

Before proceeding to a more detailed review of the pharmacology of the most important medications, please take time to consider the following fundamental considerations:

- As seen above, depending on the medication used, the effects are often complicated and not consistent even within classes. Important information to remember for each agent is the effect on the action potential duration, the effect on the refractory period and whether the agent has marked pro-arrhythmic potential. These effects can be paired with the knowledge of which ion channels are affected by each agent.

- Antiarrhythmic medications are all negatively inotropic. Combined with the anti-α and anticholinergic actions some exhibit this has the potential to cause considerable haemodynamic instability. Caution should always be exercised when using these drugs.

- The pharmacology of these medications may be modified by patient disease process and is prone to considerable drug-drug interaction.

- There is little evidence that chronic antiarrhythmic therapy improved survival in patients with cardiac disease.

Individual Antiarrhythmic Drug Pharmacology

This section will review the pharmacology of several of the most important antiarrhythmic medications. In the interest of brevity, several prototypical drugs are omitted as they are either very rarely prescribed, their real-world indications are very narrow or they are not registered for use in South Africa. Many of the references detailed at the end of this note can provide details one them as they may be asked in an examination.

Lignocaine (VW class Ib)

- Core indications
    - Life-threatening ventricular arrhythmia
    - Ventricular bigeminy, fibrillation or frequent PVCs
- Administration
    - 1-1.5mg/kg repeat after 5 minutes if required
- Mechanism of Action
    - Sodium channel blockade with little or no change in APD or ERP
- Pharmacokinetics
    - Distribution t1/2 = 8 minutes
    - Broken down in the liver, excreted in the kidneys
- Adverse effects
    - Proarrhythmic even in therapeutic doses
    - Myocardial depression in toxic doses
    - Central nervous system toxicity

Amiodarone (VW class I, II and IV)

- Core indications
    - Very broad indication for multiple arrhythmia states

  - SVTs including AF and atrial flutter (often in preference to β blockers)
  - Haemodynamically STABLE wide complex tachycardia
  - WPW syndrome
- Administration
  - 300mg loading dose IV over 5 minutes
  - 900-1200mg in 5% dextrose over 24hours
  - 5mg/kg loading in children then 5 - 25ug/kg/min
  - Glass bottle, avoid PVC tubing, CVC only
- Mechanism of Action
  - Blocks sodium, calcium and potassium channels
  - Mild blockade of α, β and ACh receptors
  - Prolongs APD and ERP
- Pharmacokinetics
  - Absorption
    - Oral: Slow, no first-pass metabolism
    - Clinical effect after 1-3 weeks
    - Half-life 28 days
    - IV: Effective in minutes to hours
  - Distribution
    - 96% protein bound
    - Significant distribution in adipose tissue
  - Metabolism and Elimination
    - Biphasic t1/2: 3-10 days then 26-107 days
    - Metabolism via CYP3A (CYP inhibition)
    - Active metabolite N-desmethyl-amiodarone
- Drug interactions
  - CYP inhibition increases concentrations of Digoxin, Procainamide and Warfarin
  - Cholestyramine increases the excretion of amiodarone
- Adverse effects
  - Acute
    - Pulmonary toxicity by induction of oxygen free radicals, made worse by high FiO2 concentrations, resembles ARDS
    - Hypotension due to a combination of negative inotropy and receptor blocking effects
    - Proarrhythmic, QT prolongation – rare, torsades de pointes
  - Chronic
    - Mimics pulmonary fibrosis, possible due to hypersensitivity pneumonitis, cessation may slow progression
    - Thyroid dysfunction, hyper- or hypothyroidism in 30% of chronic users, iodinated drug interfered with peripheral T3 conversion, thyroidectomy in hyperthyroidism may offer a solution
    - Ocular toxicity, optic neuritis and corneal deposits
    - Peripheral neuropathy

β blockers (VW class II)

- Core Indications
  - Rate control in atrial fibrillation
  - Termination of stable SVT including AF
  - Termination of ventricular arrhythmias
  - Alternative to amiodarone for rate control in WPW syndrome
- Mechanism of action
  - Competitive antagonism of β receptors
  - Decreases SA node firing rate, slows conduction in AV node and ventricles
  - Increases fibrillation threshold
- Pharmacokinetics
  - Esmolol has the most favourable intravenous kinetics
  - Distribution half-life 9 minutes
  - Hydrolysed by red cell esterases
  - Inactive metabolites

- Administration (Esmolol)
  - 0.25-0.5 ug/kg IV slow bolus
  - 50-200 ug/kg/min infusion
  - Titrated to effect
- Adverse effects
  - Contraindicated in asthma, bradyarrhythmias, acute cardiac failure, peripheral vascular disease and type 1 diabetes

Calcium channel blockers (VW class IV)

- Core indications
  - Much the same as for β blockers
  - Less popular for termination and rate control of AF
  - Not effective for termination of ventricular tachyarrhythmias
- Mechanism of action
  - Inhibit calcium flux through slow calcium channels
  - Negatively chronotropic
  - Negatively inotropic
- Pharmacokinetics
  - Both verapamil and diltiazem
    - Have poor oral bioavailability less than 45%
    - Are highly protein bound in plasma
    - Have distribution half-lives of 4-6 hours
  - Verapamil is mainly excreted unchanged by the kidneys
  - Diltiazem is metabolized in the liver to active metabolites with long half-lives
- Drug interactions
  - Verapamil increases digoxin levels significantly in early treatment
  - Diltiazem increases free fraction of carbamazepine
- Adverse effects
  - Synergistic with volatile anaesthetics (also Ca channel blockers)
  - Symptomatic hypotension and reflex tachycardia
  - Oedema, constipation, rashes
  - May precipitate cardiac failure in poor LV function

Adenosine

- Core indication
  - Highly effective in termination of supraventricular tachycardias except for AF and atrial flutter
- Mechanism of action
  - Directly activates an adenosine sensitive outward potassium channel in the SA and AV nodes resulting in profound slowing of conduction and firing rate
  - Marked prolongation of nodal refractory period terminates SVT
  - Coronary vasodilatation from A2 receptor stimulation
- Pharmacokinetics
  - Half-life of 10 seconds due to uptake into RBCs and endothelium and phosphorylation to AMP
  - Results in rapid onset offset kinetics
- Drug interactions
  - Caffeine blocks adenosine receptor requiring increased dose for effect

Digoxin

- Core indications
  - Treatment of cardiac failure with low ejection fraction
  - Rate control in atrial fibrillation
- Pharmacokinetics
  - Oral bioavailability around 55%
  - Excreted by the kidneys, half-life 36 hours

- Half-life in renal failure is 5 days via biotransformation

- Mechanism of action
  - Positive inotrope
    - Competes with potassium for binding to the Na/K/ATPase pumps on the cell membrane
    - Inhibits the pump resulting in a larger Na burden in the cell
    - This, in turn, increases Ca flux into the cell via the Na/Ca exchanger leading to greater calcium-dependent calcium release by the sarcoplasmic reticulum
  - Negative chronotropy
    - Dose-dependent
      - Low doses – baroreceptors sense the increased cardiac output and cause reflex slowing of SA firing rate
      - High doses – Directly suppress SA firing rate and slow conduction through the AV node. Prolongs atrial and AV nodal refractory period. PR interval may be prolonged.
  - Administration
    - Rapid loading – 10-20ug/kg then repeat 5ug/kg at 6 and 12 hours until response
    - Slow loading – 5ug/kg daily for a week
    - Maintenance – 125-500ug daily. Monitor levels, maintain below 2.5ng/ml
  - Adverse effects
    - Toxicity
      - Occurs above plasma level of 2.5ng/ml
    - Cardiac effects
      - Bradycardia (often with ventricular bigeminy)
      - Atrial tachycardia with variable conductance
      - A sudden increase in ventricular response
      - Ventricular fibrillation
    - Non-cardiac effects
      - Nausea and vomiting, dizziness
      - Confusion, visual disturbances (yellow auras)
    - Hypokalaemia augments toxic effects
    - Hypercalcaemia, hypomagnesaemia, hypoxia likewise may worsen toxicity
    - Treatment
      - Administration of phenytoin or lignocaine
      - Transcutaneous or transvenous pacemaker

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Notes

Inotropes and Vasopressors

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Introduction

Inotropic and vasopressor agents are commonly used in the haemodynamic management of patients with cardiovascular compromise. Inotropes are substances that alter myocardial contractility. Positive inotropic agents will increase contractility and are used to increase cardiac output.

Vasoactive agents are substances that produce vasodilation or vasoconstriction. Vasopressors produce vasoconstriction and are used to increase blood pressure. Many positive inotropic agents also have vasoactive activity and can be classed as either inopressors, which cause increased contractility and vasoconstriction, or inodilators, which cause increased contractility and vasodilation. Selected agents in general use will be discussed below.

Classification and mechanism of action

Sympathomimetics

Sympathomimetics are agents that modulate the sympathetic nervous system by acting on adrenoreceptors or dopamine receptors. Noradrenaline, adrenaline and dopamine are endogenous catecholamines; the other sympathomimetics are synthetic.

Catecholamines function as neurotransmitters in the autonomic nervous system and hormones in the blood circulation. They are derived from the amino acid tyrosine and consists of a catechol ring and amine side chain. An α carbon is bound to the amino side chain and a β carbon to the catechol ring. The functional groups on the α carbon and terminal amine determine its selectivity and whether it acts as an agonist or antagonist at adrenoreceptors.

This action can be direct (noradrenaline, adrenaline, dopamine, dobutamine, isoproterenol, phenylephrine, metaraminol), or indirect (dopamine, ephedrine), either by stimulating the release of noradrenaline or by preventing breakdown and reuptake of endogenous sympathomimetics.

Catecholamines are metabolized by catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO) and therefore MAO inhibitors will enhance and prolong the action of catecholamines.

The effect of sympathomimetic agents depends on their receptor specificity and affinity, as well as any compensatory reflexes they may evoke. Sympathomimetics exert their effect via G-coupled receptors. A simplified comparison of relevant receptors is shown in table 1.

Receptor	Site	Mechanism	Effect
α_1	Vascular smooth muscle	G_q-coupled phospholipase C activated → ↑IP_3 → ↑Ca^{2+}	Vasoconstriction
α_2	Nervous system Platelets	G_i-coupled adenylate cyclase activated → ↓cAMP	Attenuate sympathetic activity Sedation & analgesia Platelet aggregation
β_1	Heart	G_s-coupled adenylate cyclase activated → ↑cAMP→ ↑Ca^{2+}	+ inotropy, + chronotropy + dromotropy, + lusitropy
β_2	Vascular smooth muscle, bronchi, uterus	G_s-coupled adenylate cyclase activated → ↑cAMP→ ↑Na^+/K^+ATPase activity	Vasodilation Relaxation of smooth muscle
D_1	Renal & mesenteric vascular smooth muscle, central nervous system	G_s-coupled adenylate cyclase activated → ↑cAMP	Vasodilation Modulate extrapyramidal activity

Table 1

In the myocardium, increased levels of cAMP activate protein kinase A, which then phosphorylates calcium (Ca^{2+}) channels. This promotes the influx of Ca^{2+} into the cardiomyocyte via the L-type Ca^{2+} channels, stimulating further Ca^{2+} release from the sarcoplasmic reticulum. This Ca^{2+} binds to troponin C, facilitating actin-myosin interaction that induces myocardial contraction. During diastole the myocardium relaxes as Ca^{2+}diffuses away from troponin C. In vascular smooth muscle, elevated cAMP inhibits myosin light chain kinase and this leads to vasodilation.

In addition to their action on the cardiovascular system, sympathomimetics also modulate microvascular homeostasis, metabolic rate and immune cell activation, among other effects.
The most important side effects from β receptor agonists are arrhythmias and increased myocardial oxygen consumption. It should therefore be used with caution in patients with myocardial ischaemia, despite a predictable increase in cardiac output. Prolonged use of high doses may cause focal myocardial necrosis.

The most important side effects from α receptor agonists are bradycardia, decreased cardiac output and myocardial ischaemia related to increased afterload. Excessive peripheral vasoconstriction also leads to reduced perfusion to organs and extremities.

Noradrenaline has a higher affinity for α compared to β receptors and is therefore a much more potent vasopressor than inotrope. The effect of endogenous noradrenaline is different to that of systemically administered noradrenaline. Endogenous noradrenaline has moderate β effects and leads to tachycardia and an increase in cardiac output, in addition to its significant α effects. It increases systolic and diastolic blood pressure, and therefore coronary blood flow. Systemically administered noradrenaline is more likely to act as a pure vasopressor and may cause a reflex bradycardia and decrease in cardiac output. Noradrenaline is commonly used as the first-line vasopressor for all forms of shock with associated severe hypotension.

Adrenaline is a nonselective agonist of all adrenoreceptors and is a potent inopressor. At lower doses the β effect is dominant. It is the most arrhythmogenic of all the agents and causes an increase in serum lactate levels. Adrenaline is commonly used in the treatment of cardiac arrest and anaphylaxis.

Dopamine has a high affinity for dopamine receptors, leading to vasodilation and increased coronary, cerebral, renal and mesenteric blood flow. It also has a natriuretic effect that increases urine output, but not necessarily creatinine clearance. It inhibits the release of noradrenaline in peripheral blood vessels causing vasodilation. It also inhibits the uptake of noradrenaline in presynaptic sympathetic nerve terminals, thereby causing vasoconstriction and increased myocardial contractility and heart rate. The vasoconstriction is usually dominant, so the net effect will be a mild increase in vascular tone. It directly stimulates adrenergic receptors at increasing doses, leading to more pronounced vasoconstriction and a modest increase in cardiac output.

Dobutamine is a synthetic catecholamine with an affinity for α_1 and β receptors. It acts as both an agonist and antagonist on α_1 receptors in vascular smooth muscle, but vasodilation usually dominates. It increases myocardial contractility and cardiac output due to β effects and thus functions as an inodilator. The chronotropic effect is moderate and dose related. It may cause vasoconstriction in high doses.

Isoproterenol is a synthetic catecholamine that is structurally related to adrenaline but acts almost exclusively on β receptors and functions as a potent inodilator. It has a profound chronotropic effect, limiting its use in shock not associated with bradycardia.

Phenylephrine is a pure α agonists and potent vasoconstrictor. It is useful in situations where an increase in systemic vascular resistance is required, but a tachycardia is undesirable, for example hypertrophic obstructive cardiomyopathy.

Ephedrine and Metaraminol has both direct and indirect sympathomimetic actions. Ephedrine causes pre-synaptic noradrenaline displacement and inhibits its metabolism by MAO. It also exhibits mild direct β effects.

Metaraminol increases noradrenaline concentration through pre-synaptic displacement and by competing with noradrenaline for uptake. It also has direct agonism, with mainly α_1 and very little β effects. It is used as a vasopressor but should be avoided in obstetric practice as it reduces uterine

blood flow. Tachyphylaxis may occur with the use of indirect acting agents due to the depletion of noradrenaline.

Other agents

Vasopressin

Vasopressin, or antidiuretic hormone (ADH), is released by the posterior pituitary gland in response to hypotension and hypernatremia. It is a vasoactive agent with no inotropic effects. It acts on V_1 receptors, causing vasoconstriction, and on V_2 receptors, causing vasodilation. The overall effect tends to be vasoconstriction, but this depends on the concentration of vasopressin and the location of the receptors. Vasopressin induces synthesis of nitric oxide and this may limit the vasoconstriction effect.

It increases vascular sensitivity to noradrenaline, augmenting its effects, but it may decrease myocardial β receptor sensitivity, reducing contractility. It causes mesenteric ischaemia in high doses. Exogenous vasopressin is useful to increase systemic vascular resistance while reducing in pulmonary vascular resistance and is generally used as an adjunct to other agents. It may also reverse a relative deficiency of the hormone seen in established sepsis.

Terlipressin, a prodrug, has a longer duration of action than vasopressin and a greater affinity for V_1 compared to V_2 receptors. It may cause pulmonary vasoconstriction. Selepressin, a selective vasopressin V_{1A} receptor agonist, is a potent vasopressor, and shows promise in the treatment of septic shock.

Angiotensin II

Angiotensin II is a potent vasoconstrictor that is part of the renin-aldosterone-angiotensin (RAAS) system. Stimulation of angiotensin receptors (AT_1 and AT_2) leads to vasoconstriction, as well as aldosterone and vasopressin secretion. Synthetic angiotensin II can be used in combination with noradrenaline to increase blood pressure in patients with refractory distributive shock.

Phosphodiesterase inhibitors

Milrinone and inamrinone are bipyridine derivatives and selective phosphodiesterase III inhibitors. They prevent the degradation of cAMP and cGMP by this enzyme in cardiac and vascular smooth muscle. This increases the slow Ca^{2+} inward current during the cardiac action potential and causes an increase in intracellular Ca^{2+} release, leading to positive inotropy, chronotropy and lusitropy. Its use causes vasodilation in pulmonary and vascular smooth muscle and is indicated as an inodilator, especially in the context of pulmonary hypertension and right heart failure. It causes a modest increase in heart rate but may trigger arrhythmias. Enoximone is an imidazole derivative with similar effects but demonstrates less inotropy.

Calcium sensitisers

Levosimendan is a myofilament calcium sensitizer that increases myocardial contractility without increasing intracellular Ca2+ concentration. It binds to the N-terminal of troponin C in systole, inhibiting troponin I, and prolonging the interaction of myosin and actin filaments.

It does not impair diastolic relaxation and has a more favourable effect on myocardial oxygen demand compared to other inotropes. It is also much less likely to cause arrhythmias. It also opens ATP-sensitive potassium channels in the myocardium and vascular smooth muscle. This results in vasodilatation and is cardioprotective during episodes of ischaemia. It also has anti-inflammatory properties and may decrease ischemic reperfusion injury. At higher doses it exhibits phosphodiesterase III inhibition.

Nitric Oxide inhibitors

Methylene blue and N-monomethyl-L-arginine modulates endothelial vascular tone by inhibition of nitric oxide, causing vasoconstriction. It has been used in the treatment of refractory distributive shock, but its use is limited by an associated reduction in heart rate and cardiac output.

Novel inotropes targeting sarcomeres, ion pumps and excitation–contraction coupling that appear promising with current available data include omecamtiv mecarbil (OM), istaroxime and nitroxyl

Commonly used vasoactive agents are summarised in table 2.

Table 2. A comparison of selected commonly used vasoactive agents (HR = heart rate, Con = contractility, SVR = systemic vascular resistance, PVR = pulmonary vascular resistance, MAP = mean arterial pressure, CO = cardiac output, PDE = Phosphodiesterase, $K+_{ATP}$ channel = Adenosine Triphosphate sensitive Potassium channel)

	Agent	Receptor type and affinity					Haemodynamic effects						Main utility	Dose range	Onset	t1/2	Primary elimination
		α_1	α_2	β_1	β_2	D_1	HR	Con	SVR	PVR	MAP	CO					
Inopressors	Adrenaline	3+	1+	4+	3+		↑	↑	↑	↔	↑	↑	Distributive shock Cardiogenic shock	0.01-0.4 mcg/kg/min	1 min	2 min	hepatic
	Noradrenaline	4+	1+	2+	1+		↔/↑	↑	↑	↔/↑	↑	↔/↑	Distributive shock Cardiogenic shock	0.01-0.4 mcg/kg/min	1 min	5 min	hepatic
	Dopamine	H		M	M	L	↔/↑	↑	↔/↑	↔/↑	↔/↑	↔/↑	Cardiogenic shock	<5 mcg/kg/min (L) 5-10 mcg/kg/min (M) >10 mcg/kg/min (H)	5 min	2 min	renal
Inodilators	Dobutamine	1+		4+	2+		↑	↑	↓	↓	↔/↑	↑	Cardiogenic shock	2-20 mcg/kg/min	2 min	2 min	hepatic
	Isoproterenol			4+	3+		↑	↑	↓	↔/↓	↔/↓	↑	Heart block not requiring pacing Bradycardia	0.05-0.2 mcg/kg/min	1 min	2.5 min	hepatic
	Milrinone	PDE 3 Inhibitor					↑	↑	↓	↓	↓	↑	Cardiogenic shock	0.125-0.75 mcg/kg/min	10 min	2.3 h	renal
	Levosimendan	Calcium sensitizer $K+_{ATP}$ channel activation PDE 3 Inhibitor					↑	↑	↓	↓	↓	↑	Cardiogenic shock	0.05-0.2 mcg/kg/min	5 min	1 h	hepatic
Vasopressors	Phenylephrine	3+	1+				↓	↓	↑	↑	↑	↔/↓	Distributive shock	0.25-6 mcg/kg/min	1 min	5 min	hepatic
	Vasopressin	Stimulate V1 receptor					↓	↔/↓	↑	↔/↓	↑	↔/↓	Distributive shock	0.01-0.1 U/min	1 min	10 min	hepatic

Clinical use

Inotropes and vasopressors are used to treat patients with haemodynamic compromise and shock. There are 4 main types of shock: hypovolaemic, cardiogenic, distributive and obstructive. These agents can be used in all types of shock but is usually indicated in cardiogenic and distributive shock. **The cause should be treated first and any hypovolaemia corrected.**

The use of these agents is associated with increased morbidity and mortality and should be administered as part of a care bundle, with multidisciplinary input.
They are administered intravenously via central access, with appropriate haemodynamic monitoring. Extravasation may cause skin necrosis. Some agents may be administered peripherally for a limited time (adrenaline, noradrenaline, phenylephrine, isoproterenol), but this is not recommended in higher doses and the site should be monitored.

Cardiogenic shock usually occurs in patients with acute coronary syndromes or decompensated cardiac failure. In these patients neuroendocrine activation causes vasoconstriction and tachycardia and they should be treated with an agent that has positive inotropic effects without further increasing systemic vascular resistance, such as dobutamine. However, some patients may present with significant hypotension and will require an inopressor, or the addition of a vasopressor.
Treatment is aimed at improving myocardial function and organ perfusion.

According to the current European Society of Cardiology guidelines, the use of inotropic agents should be limited to patients with hypotension (SBP <90 mmHg) and/or signs/symptoms of hypoperfusion despite adequate filling status to increase cardiac output and improve peripheral perfusion to maintain end-organ function (IIb, C).

The current recommendations are that noradrenaline and dobutamine are appropriate first line agents, with levosimendan as a second line agent or a possible alternative to dobutamine. Milrinone is indicated in patients with pulmonary hypertension and right ventricular failure. Milrinone and levosimendan is appropriate for patients with recent β blocker use. Dopamine and vasopressin should be avoided if possible as it seems to be associated with higher mortality,

In distributive shock, for example sepsis, anaphylaxis and neurogenic shock, the patient usually has a dilated vascular system with low systemic vascular resistance. The use of vasopressors is appropriate in this scenario to improve blood pressure and organ perfusion. The American College of Critical Care Medicine recommend that a MAP of 60 to 65 mm Hg is targeted to perfuse organs. Higher values may be indicated in neurogenic shock, but routine targeting of supranormal MAP values in other types of shock is not recommended.

Inotropy may also be required, as myocardial depression is common in distributive shock, in which case an inopressor is used, or an inotrope in combination with a vasopressor. Noradrenaline is the first line agent recommended for the treatment of sepsis by the Surviving Sepsis Campaign, and also for neurogenic shock.

Adrenaline is used as the initial agent in the treatment of anaphylaxis.

Pure vasopressors such as vasopressin and phenylephrine may be used in distributive shock but is not routinely recommended for first line use due to the associated risks of reflex bradycardia and a decrease in cardiac output.

Angiotensin II may be considered in patients with vasodilatory shock that do not respond to high doses of conventional vasopressors to improve blood pressure.

During prolonged shock maladaptive cardiac remodelling occurs, affecting mitochondrial function and cellular Ca^{2+} handling. Catecholamines undergo degradation and desensitization and downregulation of adrenoreceptors occurs. There are changes to metabolism, the immune response and regional blood flow. This is more pronounced in septic shock and increase the challenges posed to effective treatment.

Two recent Cochrane reviews have come to the conclusion that there is currently not enough data available to recommend any vasoactive agent above another for the treatment of shock.

The use of vasoactive agents in the acute setting of the shocked patient is usually a bridge to more definitive treatment and must be individualised according to the aetiology and clinical status of the patient. Appropriate monitoring should be used and the doses should be limited and titrated to effect to limit complications.

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Notes

Entropy

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"No one really knows what entropy is, so in a debate, you will always have the advantage".
John von Neumann

Whether inside the operating room or the radiology suite, anaesthesia will always present a complex and dynamic challenge that rarely responds well to a "one-recipe-fits-all" solution. The ability to titrate interventions and individualise therapy rely on some form of feedback. Feedback can be gathered from clinical observations or by devices designed to measure the effect. These devices have become less invasive and more sophisticated. Measurement of bioelectrical potentials is one area where technological progress has made a significant impact. Measurement and processing of electroencephalograms is one such bioelectric potential.

The origin of the Electroencephalogram (EEG)

All bioelectrical signals originate from ionic flow in tissue. Ionic flow forms the basis of function inside all excitable tissues, such as the myocardium, skeletal muscle or neural tissue. The macroscopic currents that can be measured (usually from cutaneous electrodes) are the result of summated microscopic currents. These microscopic currents originate in large populations of electrically active cell groups.[1] Cortical cell- and tissue architecture play an important role in our ability to measure EEG. A single pyramidal neuron – a neuron with a long, straight apical dendrite that extends toward the cerebral cortical layer – would have imperceivable its electrical activity from cutaneous electrodes. Fortunately, these neurons have their dendrites in a parallel arrangement (Figure 1). This results in the generation of *local field potentials*.

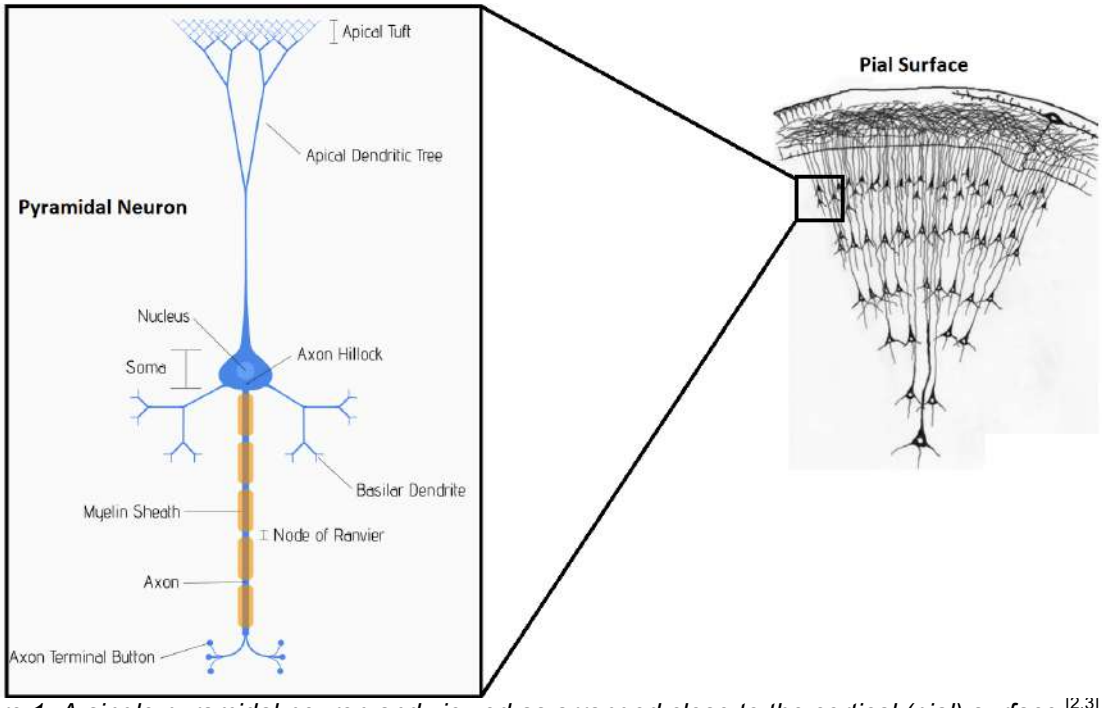


Figure 1: A single pyramidal neuron and viewed as arranged close to the cortical (pial) surface.[2,3]

Neuronal electrical activity can be divided into two categories: regenerative potentials and postsynaptic potentials. Postsynaptic potentials occur when large groups of neighbouring pyramidal neurons are exposed to neurotransmitters that alter their membrane permeability to ions and therefore change the collective membrane potential of the group. The neurotransmitters usually exert their effect by binding to selective ion channels. Activation of the ion channels can result in depolarising (excitatory) or hyperpolarising (inhibitory) membrane potentials, or a combination of both, depending

on the relative amount of inhibitory- or excitatory neurotransmitter released and their respective activated ion channels. This results in a focal electrical charge. Once the neurotransmitter release is interrupted, they are either reabsorbed or broken down. This will cause the postsynaptic potential to fade.
When two large groups of neighbouring neurons receive opposing postsynaptic potentials, their collective membrane potential will differ and this will result in a relative potential difference. These focal patches of altered membrane potentials and ionic flow, also called *local field potentials*, have magnitudes that can be measured with cutaneous scalp electrodes.[4] (See Figure 2)

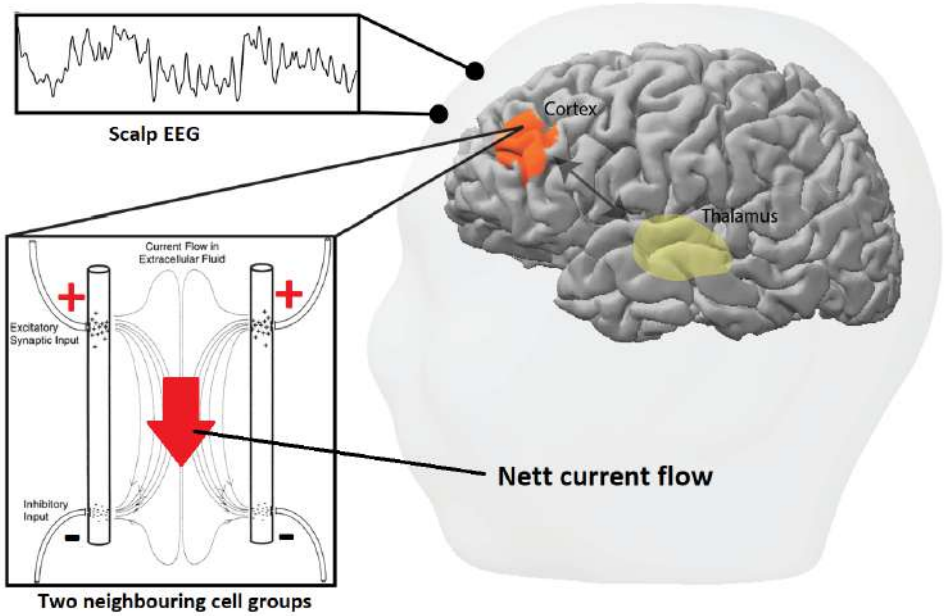


Figure 2: Two neighbouring groups of pyramidal cells with cumulative extracellular current flow.[4]

Most processed EEG monitors in current use measure EEG from frontotemporal cutaneous electrodes. The EEG patterns observed from these electrodes have distinct characteristics that alter with changes in consciousness, such as their amplitude and frequency. Table 1 shows the frequency ranges and nomenclature of clinically relevant EEG patterns. The frequency range of EEG extends from 0.5Hz to over 50Hz, although the majority of EEG signals will reside in the frequency range below 30Hz. Frontotemporal electrodes will also pick up electromyographic potentials (originating in the frontalis muscle). These frequencies are typically above 30Hz.[5]

Name	Frequency Range
Slow	< 1 Hz
Delta	1 – 4 Hz
Theta	5 – 8 Hz
Alpha	9 – 12 Hz
Beta	13 – 25 Hz
Gamma	26 – 80 Hz

Table 1: Frequency band nomenclature[4]

In the awake subject, EEG patterns have low amplitude and consist mainly of higher frequency components such as beta- and gamma waves. With increasing anaesthesia, frequency slowing along with rising amplitude occurs (see Table 2). An appropriately tailored anaesthetic state will usually yield a combination of slow, high amplitude waves (delta waves) with alpha oscillations occurring at intervals (so-called “sleep spindles”). Although the visual interpretation of these EEG patterns can appear daunting (and outside the scope of this refresher), anaesthetists should familiarise themselves with some of the basic waveforms. As with the electrocardiogram, the computed output should always be correlated with not only the visible EEG patterns but also the holistic clinical picture of the patient.

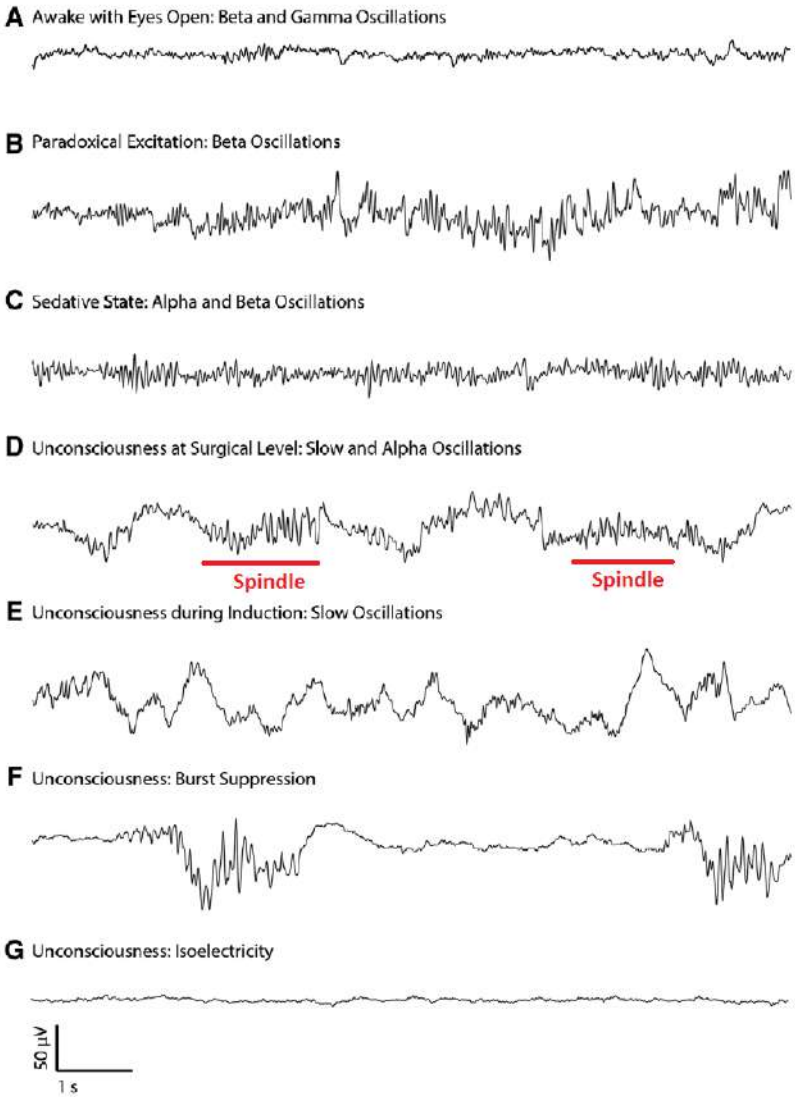


Table 2: EEG patterns during different states of consciousness[4]

EEG and anaesthesia

The effect of anaesthetic agents on cortical EEG have been studied for almost a century. Various techniques have been found to describe the degree of altered consciousness and its effect on the measured EEG. Some of these techniques relied on simple EEG processing for displaying filtered EEG patterns along with a spectrogram, while other employed complex algorithms to calculate indices (such as *state-* and *response entropy, BIS*®, etc.) that could represent a continuum of arousal level ranging from the awake subject to profound anaesthesia.[4] While visually displaying the EEG patterns requires minimal processing, their interpretation is more complex. On the other hand, EEG indices (such as *entropy* or *BIS*®) require significant processing but are easy to interpret.
Neither of these methods has become standard of practice as consciousness monitors during general anaesthesia. Reasons differ for the two different methodologies. EEG pattern interpretation requires experience and training, while EEG-computed indices have not been able to consistently prevent awareness under anaesthesia. These indices were also mostly derived from adult subjects and are therefore not directly translatable to paediatric use. They are also not able to accurately describe different drug effects on the underlying neurophysiology.[4]

Entropy

When considering entropy as a measure of the anaesthetic effect, we often assume that this statement refers to *state- and response entropy* (SERE). This refresher aims to explain how SERE is calculated and displayed. This modality was first implemented in the Datex-Ohmeda Entropy™

module, which is now part of General Electric Healthcare. There are, however, many different entropy modalities available to measure consciousness. Other entropy indices include *Shannon-, fuzzy-, sample-, approximate-, three wavelet-, permutation-, spectral entropy*, etc.[6] Each specific entropy index has its set of advantages and disadvantages. We will discuss SERE in more detail below.

To understand SERE, let us first consider what is meant by *entropy.* Entropy was first considered in the thermodynamic system. Here, it related to a physical concept: the amount of "disorder" present in the system. The exact definition of entropy is that *entropy is proportional to the logarithm of the number of microstates available in a system*. Confused yet? With a very chaotic system, where the disorder is high, the entropy is high. In this system, the number of stable microstates is high, in other words, the system has a large potential of possible states that it can be in. One could also say that the system has high unpredictability. As the disorder decreases, and more regular, predictable patterns form, entropy decreases, therefore the number of possible microstates that the system can be in, reduces. To apply this concept to EEG, where electric potentials are measured as summated signals, we can say that a chaotic system would represent one with multiple "signal generators". Large amounts of active signal generators create a chaotic EEG pattern, usually with a high frequency and a low amplitude (as the number of signal generators increases, the probability of destructive interference increases and therefore decreases the amplitude). In the awake state, more signal generators are active, increasing the number of stable microstates. As anaesthesia increases, the number of signal generators will decrease, resulting in a more rhythmic and predictable electrical signal. The number of stable microstates decreases and therefore the whole system has more predictable patterns and therefore a decrease in entropy.

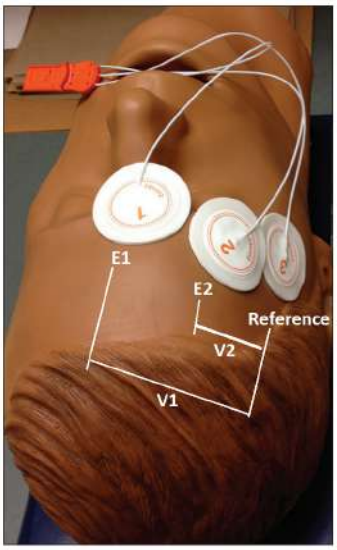
Shannon was the first to use this concept in information theory.[5] Entropy can be used to describe a signal's complexity and the *unpredictability characteristics* thereof. If the signal has a completely regular pattern, such as that of a repetitive simple sine wave, its entropy would be zero and therefore have complete predictability. As the unpredictability of the signal increases, so does its entropy.
EEG has a set of characteristics that can be used to distinguish its entropy, such as *amplitude*, *frequency* and how these characteristics vary over *time*. To compute entropy based on the time domain, *approximate- and Shannon entropy* can be used. The frequency-domain requires *spectral entropy*. SERE is a modality based on a combination of these indices.[5]

Signal acquisition and processing[1]

Being able to compute or interpret bioelectrical potentials, accurate signal acquisition is required. This entails appropriate sampling rate, signal amplification and artefact removal. EEG potentials are measured in microvolts and are therefore subject to significant amplification which makes them vulnerable to interference from not only other biopotentials (such as the electrocardiogram and electromyographic activity) but also other sources of electromagnetic energy, such as electrical instruments in close proximity. The power line alternating current (AC) providing mains electrical supply to most of the electrical instruments, is especially prone to causing interference.

Since the EEG signal requires significant amplification, any artefact or interference signal will be equally amplified. One method to reduce this interference is to use a *differential amplifier*. With this method, signal acquisition requires three electrodes: one reference electrode and two measuring electrodes. The reference electrode is the *common* electrode between the two measuring electrodes. Each of the measuring electrodes measures a potential difference between it and the reference electrode. Interference introduced by other electrical instruments or the mains power line, will be present at the reference electrode and therefore similar in both the measuring electrodes. The signals from the two measuring electrodes are *subtracted* from one another. This cancels out the interference patterns and amplifies the *difference* between the two measuring electrodes (see figure 3). The difference between the two measuring electrodes is regarded as the real underlying EEG pattern. The three-electrode setup, therefore, provides a single EEG channel output.

Figure 3: Common electrode setup. The potentials V1 and V2 are subtracted to eliminate artefact.



Most EEG processing devices currently rely on microprocessor units for their computational power. Raw EEG signals are measured as analogue voltages and will therefore need an analogue to digital conversion to allow digital signal processing. A true analogue signal will have a smooth transition from one state to another, with an infinite number of "steps" between the two states. Digital conversion entails taking several "snapshots" of the analogue signal. The amount of snapshots per unit time (usually per second) is called the *sampling frequency*, measured in Hertz (Hz). With a high sampling frequency, more of the original signal data is retained, but the amount of data to process increases. To be able to sample high-frequency analogue signals, the sampling frequency has to be increased. *Aliasing* occurs when the sampling frequency is too low and unable to measure a rapidly altering analogue signal (Figure 4). This leads to a distorted measured signal. To avoid aliasing, the sampling frequency needs to be at least twice the amount of the frequency measured.[1] For that reason, if the signal being investigated has a maximum expected frequency of 150Hz, the minimum sampling frequency required is 300Hz (300 samples taken per second).

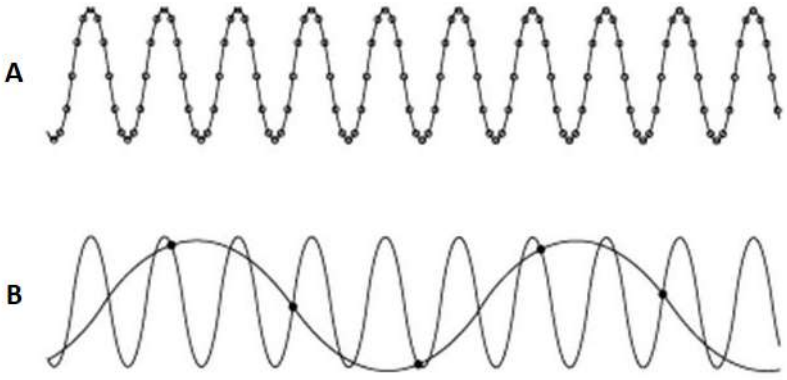


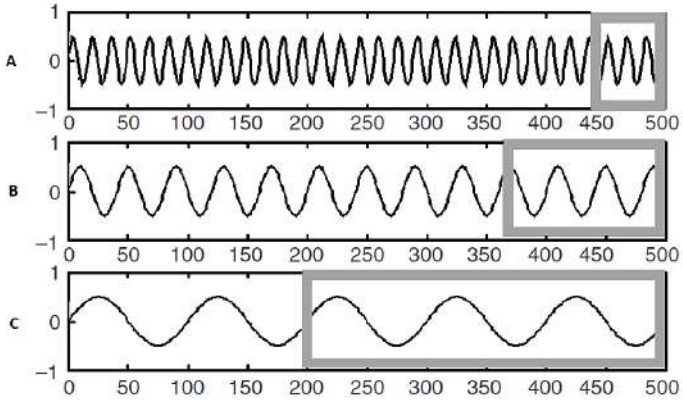
Figure 4: Aliasing. A: Appropriate sampling rate with measured samples representative of actual signal, avoiding aliasing; B: Aliasing as a result of an inappropriately low sampling rate (dots represent sampling rate) resulting in a distorted measured signal[7]

SERE uses a sampling frequency of 400Hz. This is well above the detection limit of EEG signals (highest around 50Hz) but also high enough to detect and eliminate some artefacts.

To enable the real-time computation of EEG indices, data acquisition occurs in finite time windows. These windows are called epochs. The length of the epoch has a significant impact on the ability to evaluate different frequencies and the rapidity of producing reliable data. To determine the behaviour of low-frequency data, longer epochs are required for statistically accurate calculations. Longer epochs produce data at slower intervals and can therefore slow down real-time analysis and introduce lag time. Shorter epochs produce data more regularly but are unable to analyse lower frequencies. The wide frequency range of EEG presents a challenge for fast, reliable computation. A workaround is to use different epochs to compute different frequency ranges. This is termed *time-frequency balanced spectral entropy* (figure 5) and allows for the fastest data availability.

Figure 5: Time-frequency balanced approach. A: to calculate indices for higher frequencies, a shorter window is required when compared to lower frequencies (B, C).[5]

Epoch length is therefore determined by the frequency being investigated and the sampling rate. In the SERE module (with a 400Hz sampling frequency), the shortest epoch is 1.92 seconds (which includes 768 samples). This epoch evaluates EEG frequencies between 32Hz and 47Hz. This short epoch allows for rapid detection of arousal since EEG patterns associated with wakefulness contain frequencies in this range. The longest epoch is 60.16 seconds and includes 24064 samples. EEG frequencies below 2Hz are examined by this epoch. Frequency ranges between 2Hz and 32Hz will have appropriate epoch lengths that allow rapid calculation.



Power spectrum and fast Fourier transform (FFT)

The first step of SERE processing relies on determining the spectrum of the EEG. This is often referred to as the power spectrum: it describes the *distribution of the signal power or amplitude into frequency components composing that signal.* Let us look at a simple example to illustrate this. Figure 6 shows a simple sine wave with an amplitude of one unit and a frequency of 1 Hz.

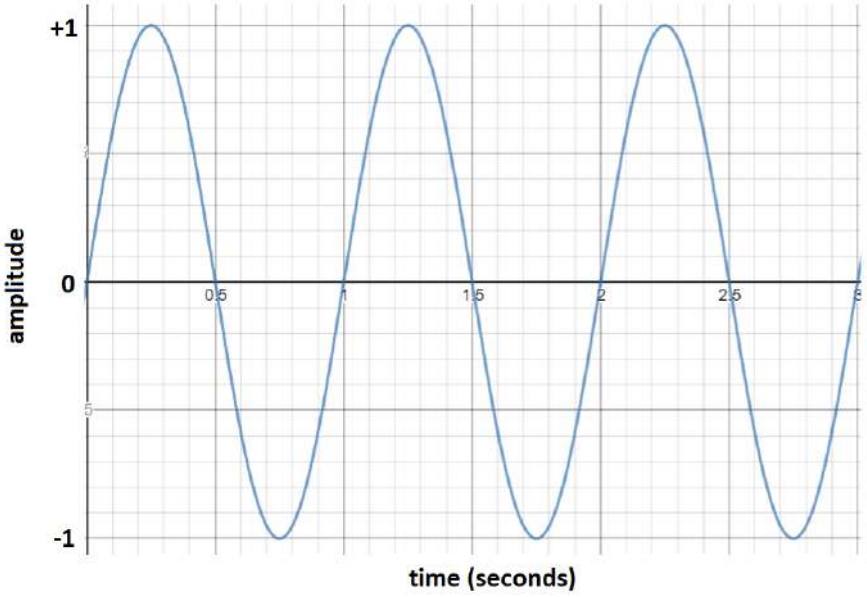


Figure 6: Simple sine wave with amplitude 1 and frequency 1 Hz

Figure 7 shows the power spectrum of the above waveform.

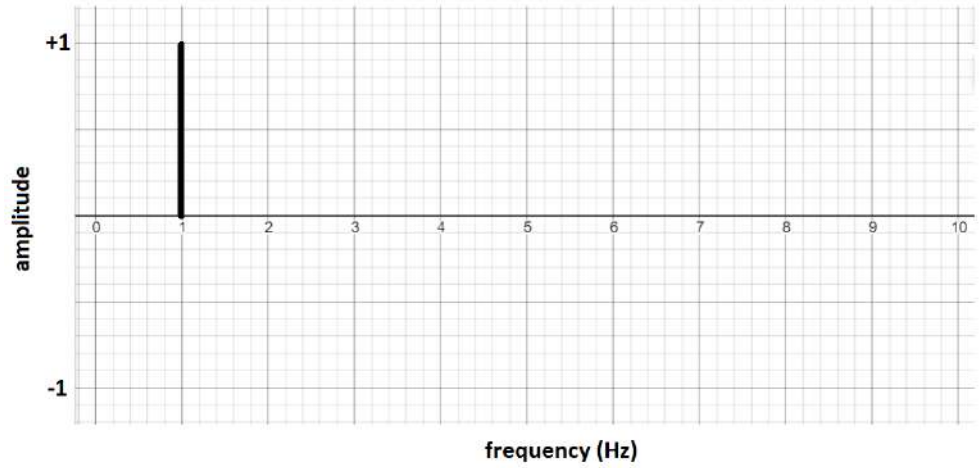


Figure 7: Power spectrum of a sine wave with amplitude 1 unit and frequency 1 Hz.

The sine wave has a uniform power spectrum with a single value. If we compare this example with another: consider a sine wave with amplitude 0.1 (a tenth of the first sine wave) and frequency 10 Hz – see figure 8.

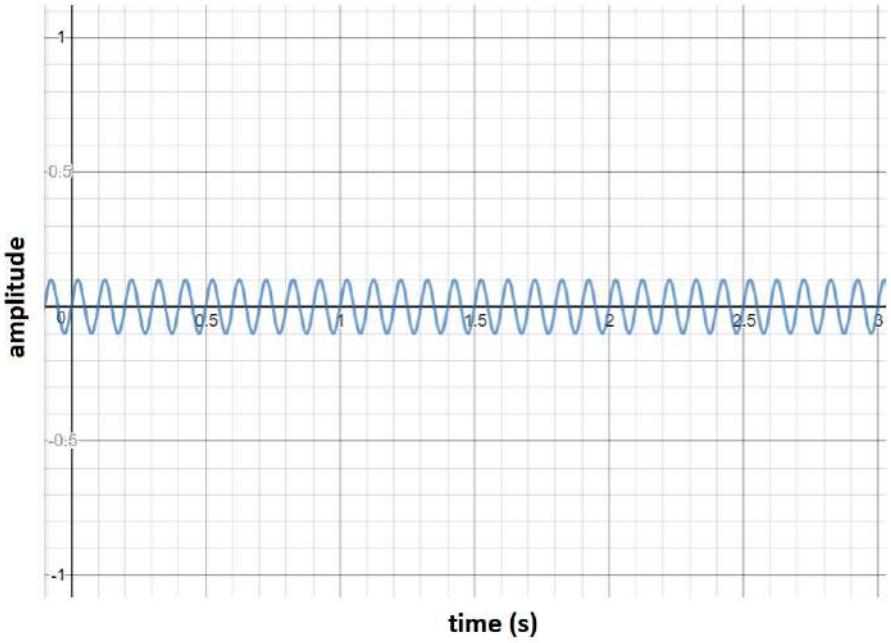


Figure 8: Sine wave with frequency 10 Hz and amplitude 0.1 units.

The power spectrum of figure 8 is represented in figure 9.

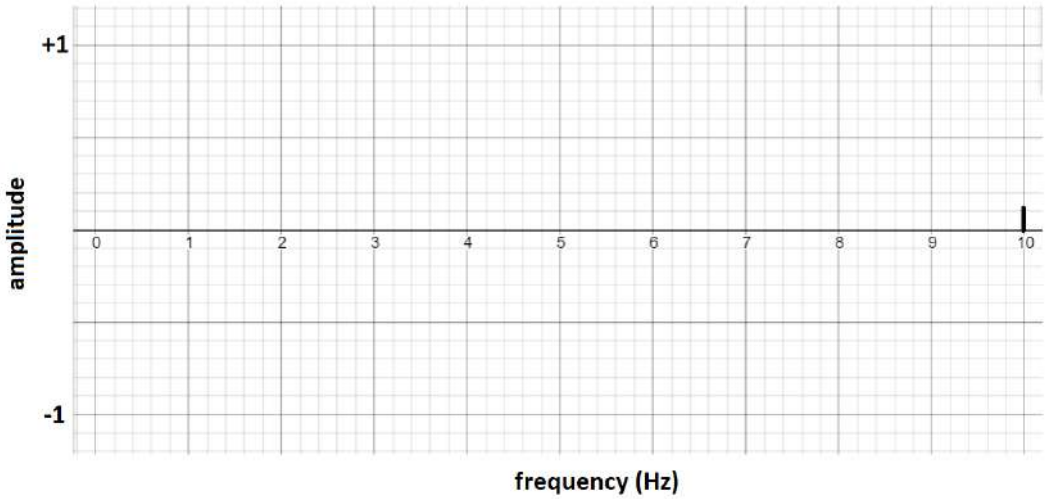


Figure 9: Power spectrum of a sine wave with frequency 10 Hz and amplitude 0.1 units.

The second example is again a simple sine wave with a uniform power spectrum, however, its amplitude and frequency have changed. Figures 6 and 8 represent amplitude vs time graphs of the EEG patterns. By converting these graphs to a power spectrum, the amplitude vs time graph is changed to an amplitude vs frequency graph – where before we had *time* as our x-axis, we now have *frequency*. Since both examples are pure sine waves, they have very simplistic power spectrum analyses. A slightly more complex example occurs when we summate the two previous examples – see figure 10.

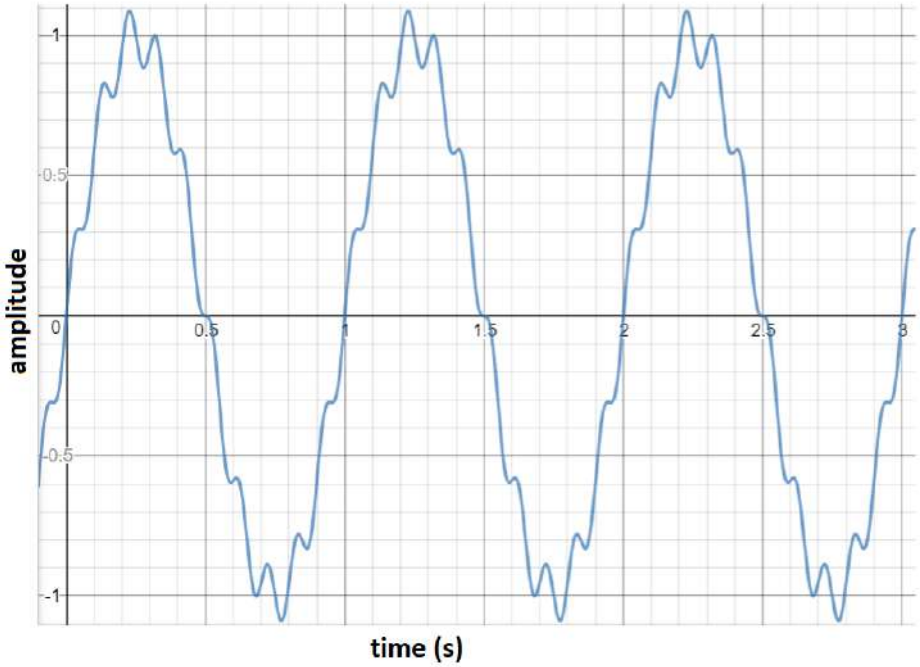


Figure 10: The net waveform when combining the waveforms of figure 3 and figure 5.

The waveform in figure 10 represents a more complex waveform. In this example, the waveform consists of two components, a sine wave of amplitude 1 unit and frequency 1 Hz summed with a sine wave with frequency 10 Hz and amplitude 0.1 units. The power spectrum of figure 10 can be represented as follows – see figure 8.

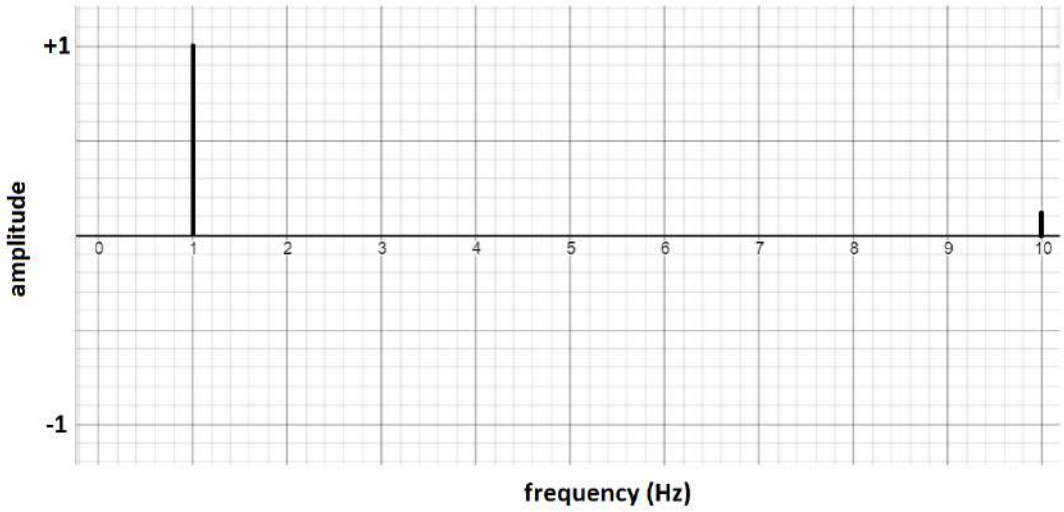


Figure 11: The corresponding power spectrum of figure 10.

The power spectrum provides information about the *power distribution* of the signal in terms of its *frequency domain*. The mathematical process for determining the power spectrum is called fast Fourier transform (FFT). Fourier's theorem states that any repetitive, arbitrary complicated time-varying waveshape can be decomposed into a sum of simple sine waves. In the following example (figure 12), the original signal is progressively decomposed into its fundamental sine wave components. Each fundamental sine wave will have a specific frequency and amplitude. This can be seen in the power spectrum.

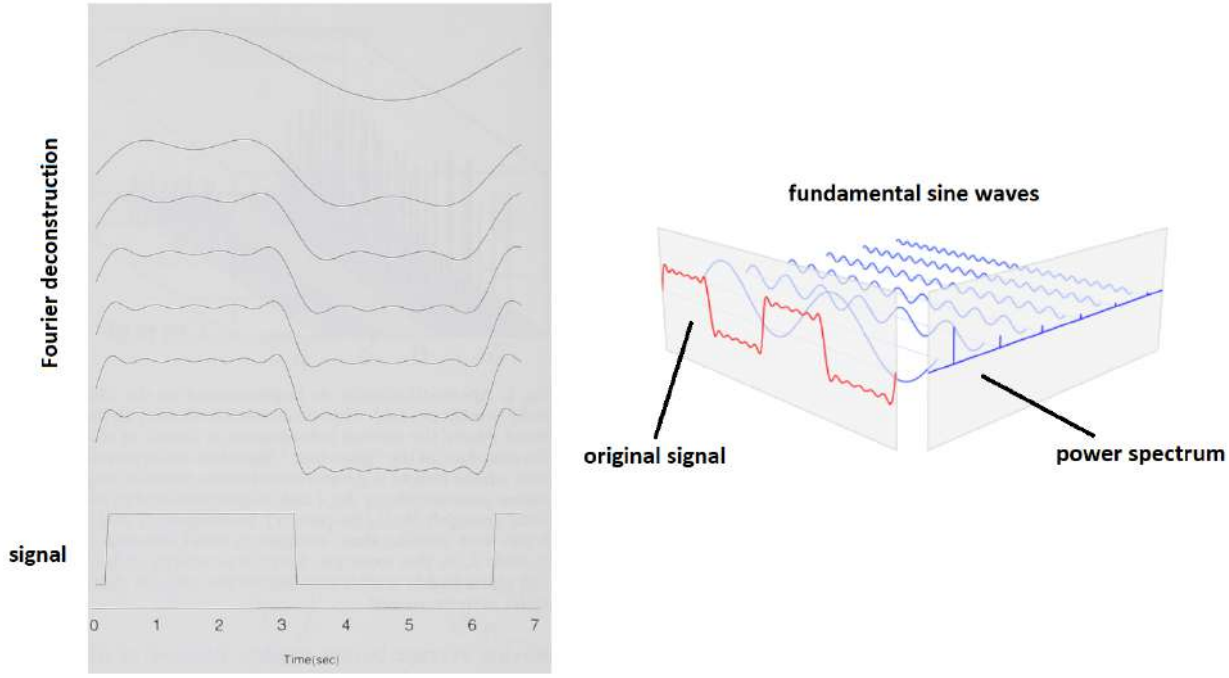


Figure 12: Fourier transform of the original signal into its fundamental sine wave functions[1,8]

The power spectrum of an EEG is notably more complex than the preceding examples. Figure 13 shows a real frontotemporal EEG signal with its corresponding power spectrum after fast Fourier transform.

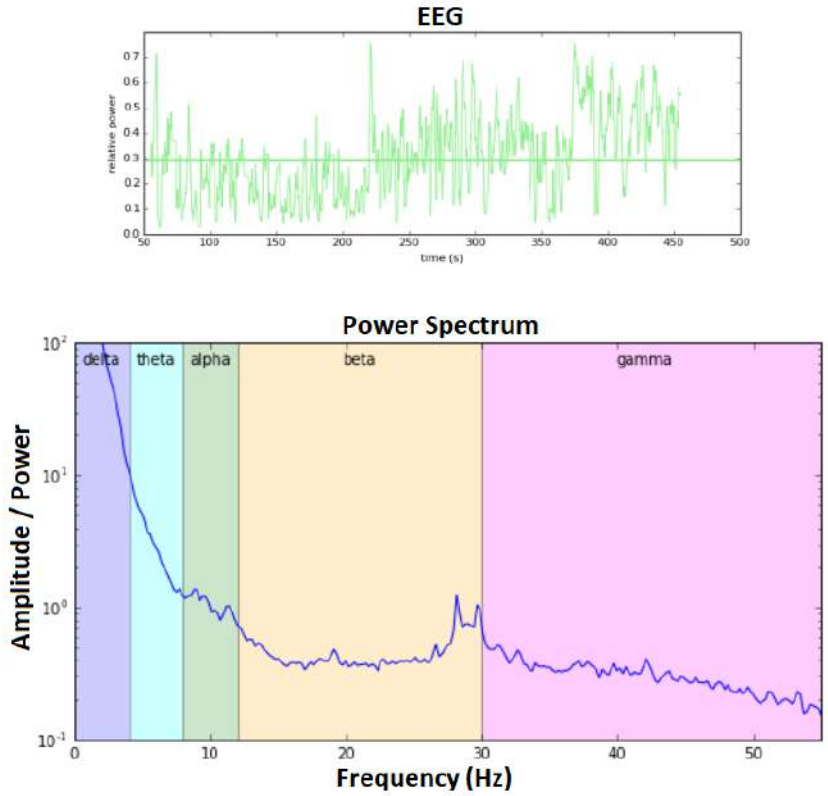


Figure 13: Example of frontotemporal EEG and corresponding power spectrum.[9]

Entropy calculation

The exact mathematical calculation of the entropy is beyond the scope of this refresher and a deep understanding thereof is not necessary. Claude Shannon published his *Shannon function* in 1948, where it was first applied in information transfer theory.[5] When this mathematical model is applied to EEG signals, it measures the predictability of future amplitude values of the EEG signal based on amplitude values already observed.[10] We will briefly discuss how SERE is calculated (a significantly simplified discussion, for sanity's sake).

Let us first look at the process of evaluating a simple sine wave with SERE. As we have mentioned before, the first step in SERE calculation includes FFT and power spectrum analysis (figure 14).

In this first step, the power spectrum is also normalised between 0 and 1. This is a crucial step since the unnormalised power spectrum will vary significantly between subjects. This variation occurs as a result of the physical characteristics of the subjects' skin, electrode placement, wire contacts, etc. All these characteristics influence the impedance of the signal and can therefore change its amplitude. By normalising the power spectrum, all subjects will have similar relative power of the signal and further signal analysis are equal between subjects. Applying the *Shannon* function to the power spectrum is the next step in SERE calculation. This function evaluates the predictability of the power spectrum and EEG signal. With our example above, the signal is completely predictable and the spectral entropy will therefore be zero (figure 15).

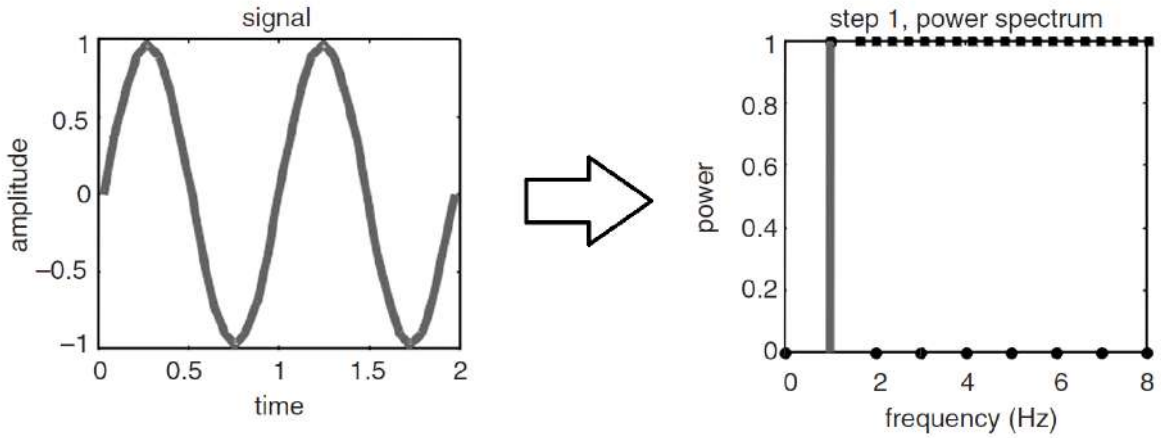


Figure 14: Step one – FFT and power spectrum of the signal

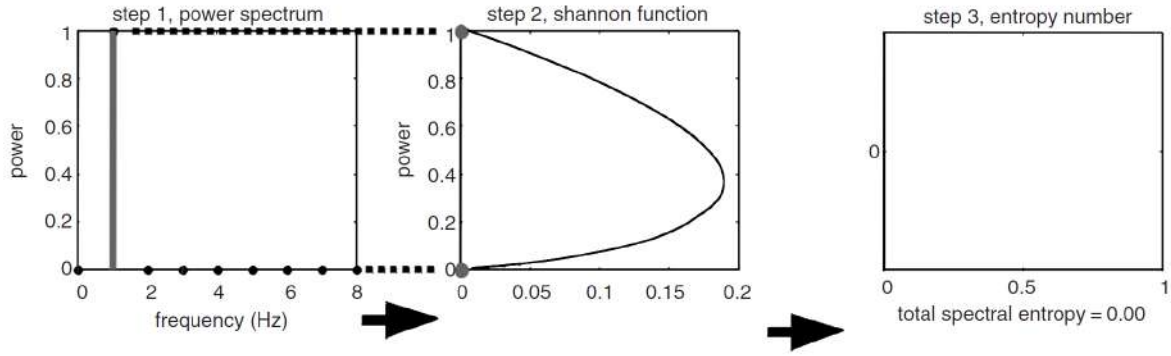


Figure 15: Stepwise calculation of the entropy number[15]

The following example shows the EEG of a patient under anaesthesia (figure 16).

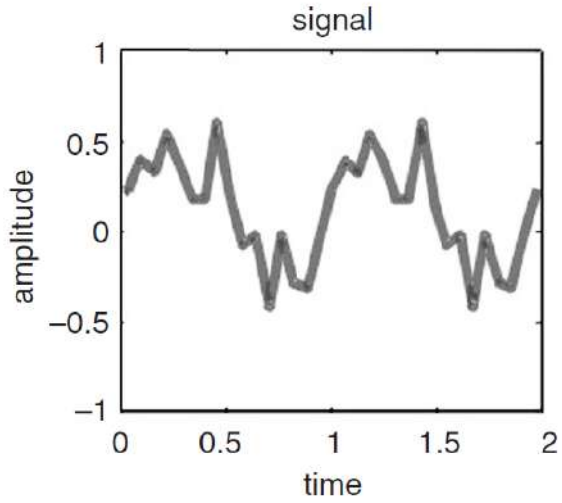


Figure 16: EEG signal from a patient under anaesthesia.

Figure 17 shows the stepwise calculation of the power spectrum, the application of the *Shannon* function and the calculation of the entropy number.

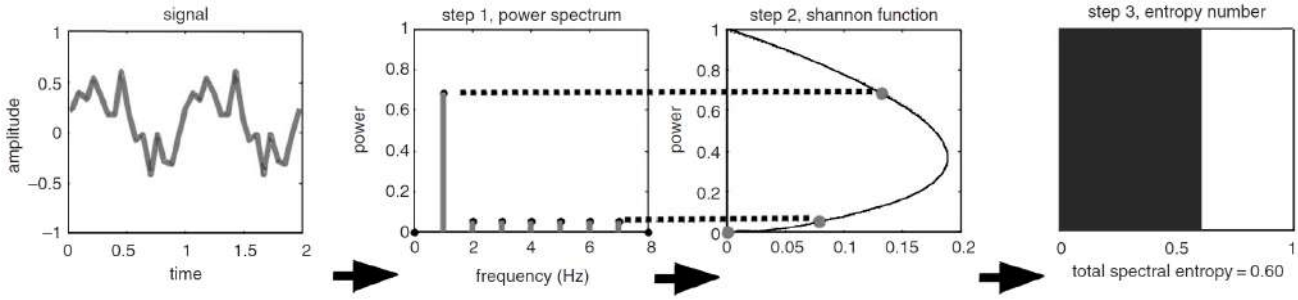


Figure 17: Entropy calculation from EEG of a patient under anaesthesia.

Understanding the mathematical detail of the *Shannon* function is not required. It aims to calculate the original signal's predictability characteristics. Since the power spectrum is normalised, the spectral entropy will also provide a normalised value of between 0 and 1. In the above example, the spectral entropy was calculated at 0.60. The next step is to change this fraction (between 0 and 1) to a simple 2 digit number. This greatly simplifies the interpretation (a number between 0 and 100 as opposed to a fraction between 0 and 1). To add more usability to the entropy reading, it is scaled (figure 18). This scaling is applied to increase the resolution of clinically relevant entropy ranges, specifically the range indicating anaesthesia and emergence. Note the steep part of the curve is in the range of 40 – 60, which represent appropriate anaesthesia.

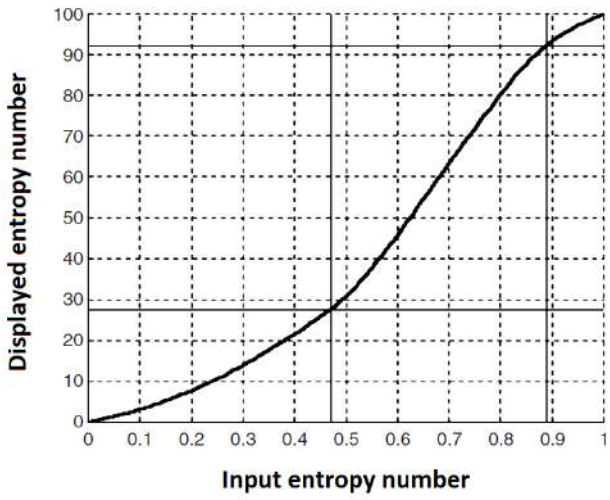


Figure 18: Adjusted entropy scale of the SERE module.[5]

The final calculation provides us with the *state- and response entropy* which can be read off the entropy module. This incorporates the presence of electromyographic (EMG) signals. If there is a sudden increase in EMG activity, it could indicate a response to a surgical- or unpleasant stimulus and likely indicative of insufficient anaesthesia. EMG signals occur mainly in the higher frequency ranges above 30Hz and can therefore be readily distinguished from EEG signals. *State entropy* represents entropy from EEG signals alone and is therefore calculated over the frequency range from 0.8Hz to 32Hz. *Response entropy* is calculated similarly but includes frequencies up to 47Hz and therefore EMG activity.[5] These two entities are therefore equal, as long as no EMG activity is present (figure 19). EMG activity will lead to increases in *response entropy* and result in an unequal *state- and response entropy*. The clinician can then interpret this as insufficient analgesia and consider the administration of additional analgesic drugs or increasing the anaesthetic depth. The suggested anaesthetic range for *state entropy* is between 40 and 60. The manufacturer recommends increasing the anaesthetic depth if the state entropy increases above 60. A *response entropy* increase of more than 10 units above *state entropy* is considered indicative of insufficient analgesia.[10]

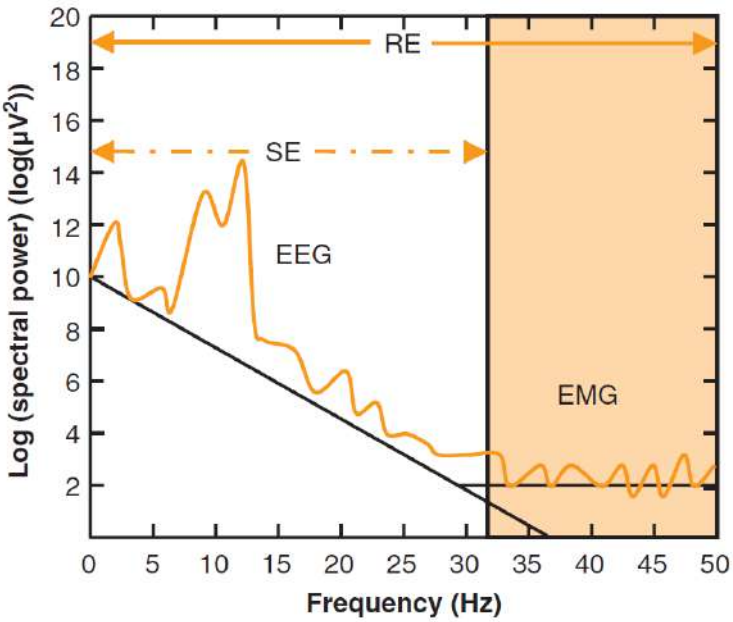


Figure 19: State- and response entropy frequency range.[10]

Burst suppression patterns occur during profound anaesthetic states (Wave F in Table 2). These patterns set in just before the absence of electrical activity (cortical silence). These patterns represent periods of increased electrical activity (burst) followed by an absence of signal (suppression). SERE calculations during burst suppression are similar to those during "lighter" anaesthetic states. The entropy calculated during the suppressed signal will, however, be zero since it has complete predictability. The burst suppression ratio (BSR) can be displayed on the entropy module. This value (between 0 and 100) represents the percentage of 0.05-second epochs out of 60 seconds that contains suppressed signal.[5] Burst suppression is usually indicative of excessive anaesthesia.

Artefact removal

As artefact has significant detrimental potential, SERE employs several methods to remove unwanted artefact. To accurately discern the presence of artefact, a very short epoch of 0.64 seconds is used. This allows the module to detect electrocautery, ECG, pacer and movement artefacts. The module then decides to reject the signal if excessive artefact is detected, using predetermined algorithms to classify the signal as contaminated or not.[5]

Summary

Entropy, and specifically SERE, attempts to provide the anaesthetist with additional information about appropriately tailored anaesthesia for the individual patient. There is no doubt that it does add significant information, but also suffers from significant shortcomings. As long as those are considered, utilising SERE could increase safety and efficiency in the theatre environment.

To briefly highlight the steps of entropy calculation:

1. Cortical neurons are arranged in such a way that post-synaptic potentials can be detected by cutaneous electrodes.
2. These potentials are caused by ionic flow as a result of local field potentials.
3. EEG and EMG signals are detected, amplified and filtered from frontotemporal electrodes.
4. The power spectrum is determined from fast Fourier transform.
5. The power spectrum is then subject to the *Shannon* function which calculates the entropy number between 0 and 1 as a fraction, based on the predictability characteristics of the signal.
6. The entropy number is then scaled to a more rapidly perceivable number (between 0 and 100).

7. *State entropy* is calculated based on frequencies between 0.8Hz and 32Hz and represents the state of unconsciousness – EEG only.
8. *Response entropy* is calculated on frequencies between 0.8Hz and 47Hz (includes EMG activity) and represents the adequacy of analgesia, with RE > 10 above SE indicative of insufficient analgesia.
9. Burst suppression is indicative of excessive anaesthesia and is represented as a percentage of suppressed signal per 60-second interval.
10. The SERE modality utilises several artefact removal algorithms to deal with electrocautery-, ECG-, pacer- and movement artefact.

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Notes

Antiemetics and the CRTZ

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Outline of this talk

- The physiology of nausea and vomiting
- Antiemetics
- Management strategies for PONV

Postoperative nausea and vomiting (PONV) are an important and common cause of patient dissatisfaction in the postoperative period. It is defined as 'any nausea, retching, or vomiting occurring during the first 24-48 hours after surgery'.[1] With a reported incidence of around 20 to 30% after surgery, and up to 80% in high-risk patients, risk assessment and prevention of PONV should be part and parcel of every anaesthetic.[1,2]

Apart from patient discomfort and negative psychological impact, additional physical consequences of PONV include oesophageal tears, increased surgical site bleeding, incisional hernia or wound dehiscence, and aspiration pneumonia if reflex glottic closure is impaired in the early postoperative period. Prolonged vomiting may also result in dehydration and associated metabolic and electrolyte disturbances.[2]

There are various risk factors for PONV that have been identified, and specific risk stratification and risk reduction strategies are discussed later in the text.

The physiology of nausea and vomiting

The physiology of nausea and vomiting is complex and is coordinated by the vomiting centre (VC) under the influence of multiple inputs.

The VC is located in the lateral medullary reticular formation of the brainstem, within the blood brain barrier (BBB).[3,4] It has high concentrations of muscarinic M_1 receptors, histamine H_1 receptors, and serotonin $5HT_3$ receptors.
Essentially, the VC receives input from four main sources:

1. The chemoreceptor trigger zone CRTZ: a v-shaped band of tissue on the lateral walls of the fourth ventricle in the area postrema (AP). It is a circumventricular organ that lies outside the BBB and is rich in receptors that induce emesis. The tissue of the CRTZ is highly specialized, composed of glia and neurons with a thin ependymal covering that is penetrated by convoluted capillaries with very loose endothelial junctions, making it sensitive to endogenous and exogenous chemical stimuli in the blood as well as the cerebrospinal fluid.[4] Blood flow velocity in the capillaries of the CRTZ is slow, which extends the time that blood, messengers, and toxins are in contact with potential receptors. Receptors here include dopamine D2 receptors, serotonin $5HT_3$ receptors, neurokinin 1 (NK1) receptors, and opioid (mu and kappa) receptors. Once these receptors detect emetic agents in the blood or CSF, the VC is triggered which is responsible for the vomiting reflex. The CRTZ is an important target in the management of PONV.
2. The vestibular system: afferents from the vestibular nuclei via cranial nerve VIII mediate the nausea and vomiting of motion sickness. It is rich in muscarinic and H1 receptors
3. The gastrointestinal tract (GIT) via sympathetic and vagal afferents.[2,3] Vagal afferents from the GIT may be mechanoreceptors (located in the muscular wall of the gut) which are stimulated by contraction and distension of the gut, or chemoreceptors (located within the mucosa) which react to intraluminal factors such as pH, temperature and other irritants.

4. Higher centres in the cortex and thalamus: play a role in vomiting due to psychiatric disorders, emotions, stress/anxiety, smells, and tastes. Poorly defined role of the limbic system and diencephalon in this response.

When the receptors in the CRTZ detect emetogenic substances in the blood or CSF, or when GIT vagal afferents are stimulated, this information is relayed to the nucleus tractus solitarius (NTS). The vestibular system communicates with the NTS via histamine H1 and acetylcholine receptors, and the cerebral cortex is thought to communicate directly with the NTS via several types of neuroreceptors. The VC ultimately orchestrates the complex act of vomiting through neural networks in the NTS that control respiratory, salivary and vasomotor centres, culminating in a series of motor events involving autonomic and somatic divisions of the nervous system.[2,4]

The prodrome is characterized by nausea, sweating and tachycardia which are sympathetically mediated, and salivation mediated by parasympathetic nerves. There is relaxation of the proximal stomach in conjunction with retrograde small bowel contraction, both vagally mediated. Oral expulsion usually follows, often associated with retching, both of which involve contraction of abdominal and diaphragmatic muscles resulting in compression of the stomach.

The CRTZ plays an important role in opiate induced PONV. Opioids stimulate D2 receptors in the CRTZ, which can effectively be blocked by phenothiazines (see below). Radioligand binding studies have shown that there is a high density of $5HT_3$ receptors in areas known to be involved in the emetic reflex, specifically on vagal afferents in the GIT mucosa, and within the brain stem, NTS and AP. Enterochromaffin cells of the GIT mucosa contain vast amounts of serotonin which is released by cytotoxic drugs or radiation. It is thought that abdominal and gynaecological surgery cause release of serotonin which stimulates $5HT_3$ receptors of vagal afferents.

Antiemetics

Many of the earlier drugs used to prevent or treat emesis (antagonists of dopamine, histamine and muscarinic receptors) were initially developed for other indications but were later found to have some antiemetic properties. Unfortunately, the side effects of many of these drugs restrict their effective use as first line prophylactic antiemetics.

Because of the complex physiological interplay between neurotransmitters and receptors, and because no single antiemetic agent can reduce the incidence of PONV to zero, the prevention and treatment of PONV should target more than one receptor type.[3] First-line agents, namely serotonin antagonists, corticosteroids, and dopamine antagonists have similar efficacy against PONV and although they act independently, they have additive effects when used in combination.

From a pharmacological aspect, there are five neurotransmitter receptor types of importance and antiemetics can therefore be classified based on their site of action:

1. Muscarinic M_1 receptors
2. Dopaminergic D_2 receptors
3. Histaminic H_1 receptors
4. Serotonergic $5HT_3$ receptors
5. Neurokinin NK1 receptors

1. Antimuscarinic drugs

- Receptor: predominantly muscarinic M_1 receptors in the VC
- MOA: Blocks *input* from CRTZ; useful against chemical stimulants, labyrinthine disorders, motion sickness; attenuates visceral reflex vomiting
- Many drugs with antimuscarinic effect have activity at one or more other receptors
- Drugs in this class:
    - *Hyoscine/scopolamine*
        - The major anticholinergic drug that is an effective antiemetic
        - Predominantly used as prophylaxis against motion sickness, but has use in vertigo and PONV, particularly in PCA pumps. Transdermal scopolamine is effective as prophylaxis against PONV.
        - A naturally occurring tertiary amine that is able to cross BBB – central effects include sedation, ataxia/dizziness, hallucinations.

- *Buclizine* (a phenothiazine hence also has antidopaminergic activity)
- (Promethazine, cyclizine, cinnarizine: see antihistamines)

2. Antidopaminergic drugs[5,6]

- Receptor: dopamine D_2 receptors
- Drugs are divided into 3 classes:
  - Phenothiazines
    - Anti-psychotics with a limited role in the treatment of N&V
    - Block central dopamine receptors therefore effective for opioid-induced nausea
    - Also block a multitude of other receptors
    - All are sedating, and have extrapyramidal side effects and anticholinergic effects of varying degrees
    - Propylamine - *Chlorpromazine*
    - Piperidine - *Thioridazine (not used for PONV)*
    - Piperazine – *Prochlorperazine (Stemetil)*
  - Butyrophenones
    - As well as blocking D_2 receptors, butyrophenones cause neurolept anaesthesia at higher doses
    - *Droperidol*
      - Antiemetic effect achieved at very low doses (0,0625-0,125 mg/kg) Recommendation to keep to total dose of below 1 mg.
      - Short plasma half-life therefore given near end of surgery
      - FDA black box warning for potential prolongation of QT_c interval, although the black box label is not for doses used in the perioperative period. The risk of sudden cardiac death was seen in doses in excess of 25 mg. At recommended doses of 0,625 – 1,25 mg, only transient QTc prolongation is seen which is comparable to that seen with ondansetron. Also, ondansetron and droperidol may even be given in combination with no worse QT prolongation than when drugs are given alone
    - *Haloperidol*
      - A butyrophenone derivative
      - Not FDA approved as an antiemetic but increased in popularity after droperidol black box warning
      - Low dose 0,5 – 2 mg effective as prophylaxis
      - Side effects: sedation, QT prolongation
  - Benzamides
    - *Metoclopramide*
      - Action on multiple receptors results in complex mechanism of action
      - Promotes gastric emptying by sensitizing smooth muscle of the GI tract to ACh
      - $5HT_4$ receptor stimulation is prokinetic
      - Anti-emetic effect is due to antidopaminergic activity at central CRTZ and peripheral dopamine D2 receptors
      - Non-sedating, but may cause EPSEs as it crosses the BBB
      - Useful in radiation sickness, PONV, drug-induced N&V, and metabolic causes of vomiting
      - 10 mg dose thought to have little or no effect on PONV (concerns regarding fabricated studies), but 25 to 50 mg has similar efficacy compared with other antiemetics, obviously with more risk of side effects (EPSE at higher doses)

3. Antihistaminergic drugs

- Receptor: H_1 receptors
- Primarily used in motion sickness
- Drugs in this class:
  - *Cyclizine*

        - A piperazine derivative hence some antidopaminergic activity
        - Also has significant antimuscarinic properties because of its large size
    - *Promethazine (Phenergan)*
        - A phenothiazine derivative
        - Also has significant antimuscarinic properties
        - Blocks input at VC and CRTZ
        - Very sedating
        - Caution with intravenous injection

4. Antiserotonergic drugs

- Receptor: $5HT_3$ receptors
    - Receptor type: ligand-gated ion channel
    - The $5\text{-}HT_3$ receptor is the only of the 7 families of serotonin receptors which is an ion-gated channel (the rest are all G-protein coupled receptors)
    - Activation results in excitatory effects mediated via ion channels which control the influx of Na^+ and K^+ ions
    - There is a high density of $5HT_3$ receptors in the CRTZ, and it is at these central locations that the potent anti-emetic effects are mediated. They also block $5HT_3$ receptors peripherally on extrinsic intestinal vagal and spinal afferent nerves.[4]
- Metabolism: first 4 are metabolized hepatically and eliminated by renal and hepatic excretion. No dose reduction in necessary in geriatric patients or renal insufficiency. Reduce dose of ondansetron in hepatic insufficiency.
- Drugs in this class:
    - *Ondansetron*
        - Prevention dose: 4mg IV at end of surgery or 8mg oral disintegrating tablet with 50% bioavailability
        - Maintenance dose 0.1 mg/kg to a max of 8 mg, eight hourly
        - Considered the "gold standard" in management of PONV prophylaxis or treatment[6]
        - NNT: 6 and 7 for the prevention of vomiting and nausea respectively
        - NNH: 36 for headache, 31 for elevated liver enzymes, 23 for constipation
        - More efficacious than metoclopramide and dexmedetomidine
        - Similar effectiveness compared to dexamethasone 4-8mg
        - Less efficacious than granisetron, ramosetron, palonosetrum, aprepitant, and fosaprepitant
        - Broken down by CYP enzymes 1A2, 2D6, and 3A4, therefore potential for drug-drug (D-D) interactions
    - *Granisetron* (prevention dose: 0,35-3 mg IV at end of surgery)
        - More effective than 4 mg ondansetron IV, but similar efficacy to dexamethasone 8 mg
        - Broken down by CYP 3A4 therefore less potential for D-D interactions
    - *Dolasetron* (prevention dose: 12.5 mg IV at end of surgery – although timing may not be important)
        - Similar efficacy to 4 mg ondansetron
        - Highly specific and selective $5HT_3$ receptor antagonist, and also has low affinity for dopamine receptors
        - Concerns about QT prolongation – no longer marketed in US
    - *Palonosetron* (prevention dose: 0.075 mg IV)
        - Second generation $5HT_3$ receptor antagonist with some inhibition at NK1 receptor as well.
        - 40-hour half-life, allosteric binding, positive cooperativity, receptor internalization
        - More effective than ondansetron, granisetron, dolasetron, tropisetron, ramosetron and dexamethasone. Similar effectiveness to aprepitant.
        - Combined with sevoflurane/N_2O anaesthesia, palonosetron reduces PONV incidence as much as total TIVA
        - **Only 5HT3 antagonist that is not associated with QTc prolongation**

- *Tropisetron* (prevention dose: 2 mg at end of surgery, although larger doses have been used)
  - Competitive and selective $5HT_3$ receptor inhibitor used mostly for chemo-induced nausea and vomiting (CINV)
  - NNT 6.7 and 5 for prevention of nausea and vomiting respectively
  - Used in Europe and Asia (not licensed in the US)
- *Ramosetron* (prevention dose: 0.3 mg IV at end of surgery)
  - Second-generation $5HT_3$ receptor antagonist
  - SE: drowsiness, dizziness, muscle pain, sedation, constipation, diarrhoea
  - More effective for PONV prevention than ondansetron, but similar treatment efficacy
  - Available in Japan and SE Asia

- Outlier:
  - *Olanzapine*
    - second-generation antipsychotic that blocks $5HT_2$ receptors and D2 receptors
    - useful in CINV

5. Neurokinin-1 (NK1) receptor antagonists

- Receptor: NK1 receptors
  - Receptor type: G-protein coupled receptor
- MOA:
  - Emetogenic effects of substance P in the brainstem nucleus tractus solitarius and the area postrema are mediated through NK1 receptors
  - NK1 Receptor antagonists penetrate the BBB and are highly selective
  - Useful in acute and delayed chemo-induced emesis, and useful as prophylaxis where POV is highly undesirable (gastric & neurosurgery)[6]
  - Effect on opioid requirements currently undetermined
- Drugs in this class
  - *Aprepitant* (40 mg oral) at induction & Fosaprepitant (parenteral version – a prodrug of aprepitant)
    - Moderate inhibitors of the CYP3A4 metabolic pathway: consider dose reduction of other drugs primarily metabolized by this pathway such as midazolam, fentanyl, ARVs, anti-TB drugs, and steroids.
    - Metabolism of warfarin is enhanced
    - Half-life 40 hours[6]
    - 40 mg orally has the same PONV prevention as palonosetron, and is more effective than ondansetron
    - Provisional data from a Cochrane meta-analysis by Weidel et al suggest that aprepitant monotherapy may have similar efficacy to several combination therapies[5]
    - Not associated with QTc prolongation
    - No sedative effects
    - Limited by cost
  - *Casopitant* (150mg po at induction)
    - Not approved for PONV use
  - *Rolapitant* (70 – 200 mg po at induction)
    - Long acting with half-life of 180 hrs.
    - Not approved for PONV use
    - Moderate inhibitor of CYP2D6: avoid concomitant use with thioridazine
    - Reports of anaphylaxis, anaphylactic shock, and other hypersensitivity reactions with intravenous administration
  - *Vestipitant*

Other antiemetics

- Corticosteroids
  - *Dexamethasone*
    - 4-8 mg at the start of surgery
    - Added benefit of analgesia

        - Effective, particularly in combination with other agents
        - Concerns around safety
            - Single dose not associated with increased postoperative infections, wound infection, anastomotic leaks, bleeding, or significant hyperglycaemia (even in diabetics), or cancer recurrence[6]
        - Proposed mechanism of action[3]:
            - Depletion of GABA stores
            - Reduction of BBB permeability to emetic substances
            - Inhibition of brainstem encephalin release
            - Inhibition of central prostaglandin synthesis
            - Inhibition of serotonin synthesis and release
- Gabapentinoids
    - *Gabapentin*
        - 600-800 mg orally 1-2 hours before surgery has shown reduced postoperative pain and decreased PONV
        - Side effects include sedation, visual disturbances, dizziness, and headache. Some reports of respiratory depression therefore need to take care in combination with other respiratory depressants
- Benzodiazepines
    - *Midazolam*
        - Limited data suggests that midazolam has similar efficacy to ondansetron in prophylaxis and treatment of PONV
        - May be useful in reducing anticipatory emesis
        - Beware sedation-related adverse events
- Ephedrine
        - 0,5 mg/kg IMI near end of surgery
        - Significant reduction in PONV for 3 hours postoperatively with minimal changes in MAP and HR
        - Caution in coronary ischaemia
- Cannabinoids
    - *Dronabinol & nabilone*
        - Seem to exhibit modest antiemetic activity, but unfavourable side effect profile (vertigo, xerostomia, hypotension, dysphoria)

Non-pharmacologic prophylaxis

- Acupuncture
    - *Pericardium 6 Acupuncture Point (PC6) Stimulation* – significant reduction in the risk of nausea, vomiting, and the need for recue antiemetics; as good as pharmacological management.
- Fluids
    - Adequate hydration strategies to maintain clinical euvolaemia
        - Minimize fasting times
        - Intravenous fluids (10-30 mL/kg) reduce risk of PONV and need for rescue antiemetics
- Carbohydrate loading
    - No significant impact

Management strategies for postoperative nausea and vomiting

I would highly recommend that you read the Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting published in 2020. It provides a very comprehensive and updated guideline on risk stratification, prevention, and treatment of PONV in adults and children.

a. Risk Assessment

Established patient-specific risk factors (adults):

- Female sex

- History of PONV or motion sickness
- Nonsmoking status
- Young age

Surgeries associated with increased risk:

- Laparoscopic
- Bariatric
- Gynaecological
- Cholecystectomy

Anaesthetic risk factors:

- Volatile anaesthetics (dose-dependent, and particularly prominent in the first 2-6 hours following surgery)
- Nitrous oxide (use for over 1 hour)
- Duration of anaesthesia
- Postoperative opioids (dose-dependent, and effect lasts for as long as the opioids are used in the postoperative period)

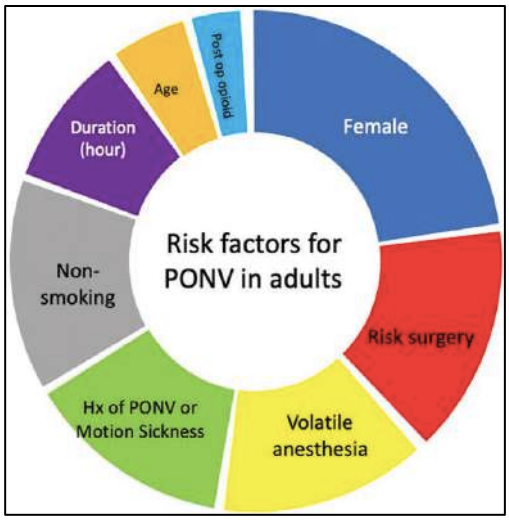

Figure 1: PONV risk factor summary in adults: the size of each segment is proportional to the OR of PONV associated with each risk factor. Permission to reproduce requested from the American Society of Enhanced Recovery.

Conflicting risk factors include ASA physical status, menstrual cycle, level of anaesthetist's experience, and perioperative fasting. Then lastly, disproven or factors of limited clinical relevance include BMI, anxiety, nasogastric tube, and use of supplemental oxygen.

Risk scores:

PONV risk scores can be used to guide prophylaxis in the perioperative period to reduce the rate of PONV, ultimately improving patient care. In adults, the Apfel simplified risk score (figure 2) is easy to remember and implement. It is based on 4 predictors, namely female sex, history of PONV and/or motion sickness, nonsmoking status, and use of postoperative opioids. The incidence of PONV with the presence of 0, 1, 2, 3, and 4 risk factors is approximately 10%, 20%, 40%, 60%, and 80% respectively. Low risk patients have 0 to 1 risk factors, medium risk have 2, and high-risk patients have 3 or more risk factors. Using risk scores to predict the incidence of PONV, we can tailor prophylaxis and enhance patient comfort and recovery.

In children, the risk factors for PONV and POV are a little different. Here we look at:

- preoperative factors (age > 3 years, history of POV/PONV/motion sickness, family history of POV/PONV, post-pubertal female);
- intraoperative factors (strabismus surgery, adenotonsillectomy, otoplasty, surgery > 30 minutes, volatile anaesthetics, anticholinergics); and
- postoperative use of long-acting opioids.

Again, number of risk factors is used to classify patient risk: patients with no risk factors are low risk, 1-2 makes one medium risk, and 3 or more risk factors designates high risk for PONV/POV.

A more simplistic approach in children (Eberhart et al) is based on 4 criteria: duration of surgery >30 minutes; age >3 years; personal or first-degree relative history of POV/PONV; and strabismus surgery. The risk of POV was 9%, 10%, 30%, 55%, and 70% with 0, 1, 2, 3, and 4 risk factors respectively.

Risk Factors	Points
Female Gender	1
Non-Smoker	1
History of PONV and/or Motion Sickness	1
Postoperative Opioids	1
Sum of points	0-4

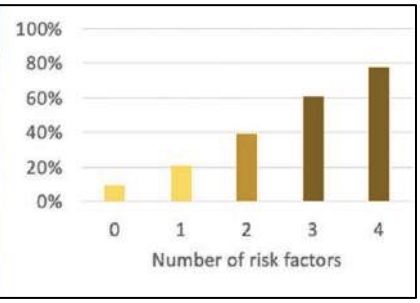

Figure 2: Apfel simplified risk score for PONV in adults
Reproduced from the Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting.

b. Reduce Baseline Risk

The following are well recognized strategies to reduce baseline risk[6]:

1. Avoidance of GA by the use of regional anaesthesia
2. Use of propofol for induction and maintenance of anaesthesia
3. Avoiding nitrous oxide in surgeries lasting more than 1 hour
4. Avoidance of volatile anaesthetics
5. Minimisation of intraoperative and postoperative opioids
6. Adequate hydration
7. Using sugammadex instead of neostigmine for the reversal of neuromuscular blockade

A few additional points on the anaesthetist's role in the prevention of PONV:

When should paracetamol be administered as part of a multimodal analgesic regimen to reduce nausea?
Give before the onset of pain!

What about the use of perioperative dexmedetomidine?
There is good evidence to suggest that systemic alpha 2 agonists such as dexmedetomidine and clonidine decrease postoperative opioid consumption and PONV.

Does neuraxial anaesthesia decrease the risk of PONV?
It depends…
Epidural anaesthesia may decrease the risk of PONV, but the use of intrathecal opioids may increase the incidence.

Just how good is propofol TIVA at preventing PONV?
Propofol TIVA is comparable to volatile anaesthesia plus single-agent prophylaxis. When combined with other prophylactic agents, propofol TIVA further reduces the risk of PONV.

Does your choice of reversal agent influence the incidence of PONV?
Neuromuscular blockade reversed with sugammadex rather than neostigmine is associated with a lower risk of PONV.

What is the benefit of running a lignocaine infusion in the prevention of PONV?
The PONV risk appears to be lower in laparoscopic abdominal procedures if a lignocaine infusion is used.

Baseline risk reduction in children

Well established in reducing baseline risk in paediatric population: TIVA, liberal fluid therapy, opioid sparing techniques (including neuraxial and regional techniques). Intravenous lignocaine has shown a reduction in POV, as well as the use of alpha-2-agonists and perioperative paracetamol.

c. PONV Prophylaxis

One of the major changes in the fourth Consensus Statement guideline is the recommendation of multimodal prophylaxis in all patients with one or more risk factors!

Various drug combinations exist for the prevention of PONV in adults and children. The choice you make will depend on drug availability, cost, and various patient factors including the risk of drug-drug interactions if the patient is on any other medication.

The Fourth Consensus Guideline for the Management of Postoperative Nausea and Vomiting has multiple useful tables on dosages and timing of drug administration, one of which I have reproduced below for your ease of reference.

Drugs	Dose	Evidence	Timing	Evidence
Amisulpride	5 mg	A2[113,114]	At induction	A2[113,114]
Aprepitant	40 mg PO	A1[115–117]	At induction	A2[118]
Casopitant	150 mg PO	A1[119–121]	At induction	
Dexamethasone	4–8 mg IV	A1[122]	At induction	A1[122]
Dimenhydrinate	1 mg/kg IV	A1[124–126]		
Dolasetron	12.5 mg IV	A2[127–129]	End of surgery; timing may not affect efficacy	A2[128]
Droperidol[a]	0.625 mg IV	A1[120,121]	End of surgery	A1[122]
Ephedrine	0.5 mg/kg IM	A2[122,124]		
Granisetron	0.35–3 mg IV	A1[125,126]	End of surgery	A1[127–129]
Haloperidol	0.5 to <2 mg IM/IV	A1[140]		
Methylprednisolone	40 mg IV	A2[141]		
Metoclopramide	10 mg	A1[142]		
Ondansetron	4 mg IV 8 mg PO or ODT	A1[142,144]	End of surgery	A1[145]
Palonosetron	0.075 mg IV	A1[146–148]		
Perphenazine	5 mg IV	A1[149]		
Promethazine[a]	6.25 mg	A2[150,151]		
Ramosetron	0.3 mg IV	A1[152]	End of surgery	A2[153]
Rolapitant	70–200 mg PO	A3[152]	At induction	
Scopolamine	Transdermal patch	A1[154,155]	Prior evening or 2 h before surgery	A1[156]
Tropisetron	2 mg IV	A1[157]	End of surgery	

These recommendations are evidence-based and not all the drugs have an FDA indication for PONV. Drugs are listed alphabetically.
Abbreviations: FDA, Food and Drug Administration; IM, intramuscular; IV, intravenous(ly); ODT, orally disintegrated tablet; PO, per os; PONV, postoperative nausea and vomiting.
[a]See FDA Black box warning.

Table 1: Antiemetic doses and timing for prevention of PONV in adults.
Reproduced from the Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting.

- Adults
  - 5-HT_3 receptor antagonists + dexamethasone
    - Ondansetron: (A1)[158,159]
    - Palonosetron: (A2)[160–162]
    - Ramosetron: (A2)[163,164]
    - Granisetron: (A3)[167]
    - Tropisetron: (A3)[168]; with methylprednisolone (A3)[169]
  - 5-HT_3 receptor antagonists + aprepitant
    - Ondansetron: (A2)[170,171]
    - Ramosetron: (A3)[172]
    - Palonosetron: (A3)[173]
  - Aprepitant + dexamethasone: (A2)[174,175]
  - 5-HT_3 + droperidol
    - Ondansetron + droperidol: (A3)[176]
    - Granisetron + droperidol: (A3)[177]
    - Palonosetron + droperidol: (A3)[178]
  - Other 5-HT_3 combination therapies:
    - Ondansetron + haloperidol: (A3)[179]
    - Haloperidol + dexamethasone + ondansetron: (A3)[180]
    - Ondansetron + betahistine: (A2)[181,182]
    - Ramosetron + gabapentin: (A3)[183]
    - Midazolam + ramosetron: (A3)[184]
  - Other antidopaminergic combination therapies
    - Dexamethasone + haloperidol: (A2)[185,186]
    - Metoclopramide + dimenhydrinate: (A3)[187]
    - Amisulpride +1 nondopaminergic antiemetic: (A3)[188]
    - Haloperidol + midazolam: (A2)[189,190]
  - Acupoint stimulation + pharmacoprophylaxis: (A2)[191,192]
  - Others
    - Propofol + dexamethasone: (A3)[193]
    - Dexamethasone + dimenhydrinate:[194] (A3)
    - Gabapentin + dexamethasone: (A3)[195]
- Children
  - Ondansetron + dexamethasone: (A1)[196]
  - Ondansetron + droperidol (A3)[197]
  - Tropisetron + dexamethasone (A3)[198]

Abbreviation: 5-HT_3, 5-hydroxytryptamine 3.

As in adults, the use of combination therapy is most effective for children at risk for POV/PONV. Multiple pharmacologic combinations exist. As mentioned earlier, the choice you make for your patient should be guided by patient comorbidities, patient PONV risk, cost, drug availability and ease of administration.

Table 2: Pharmacologic combination therapy for adults and children.
Reproduced from the Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting

d. Rescue treatment

For PONV in patients who did not receive prophylaxis, 5HT3 receptor antagonists are first line, as is promethazine 6,26 mg IVI. Haloperidol shows a comparable treatment response but with often unwanted sedation.

When PONV prophylaxis has failed, use a drug from a different class to what was used for prophylaxis if within 6 hours of prophylactic dose.

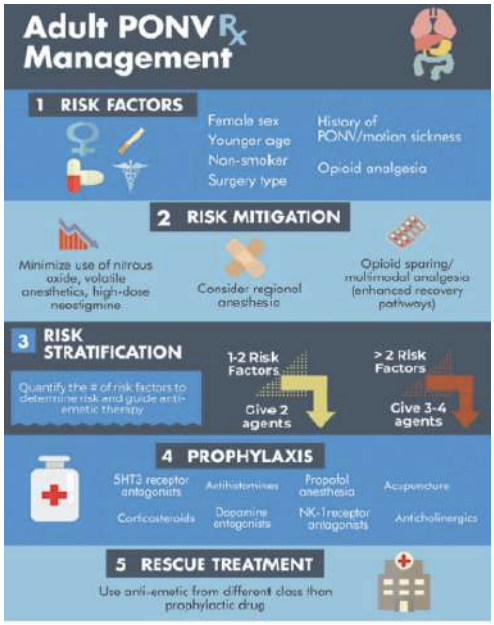

Figure 3: Algorithm for PONV management in adults.
Permission to reproduce requested from the American Society of Enhanced Recovery.

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Notes

Physiology of the Left Ventricle

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Introduction

The heart muscle orientation, cartilaginous skeleton, valves, blood supply, and conduction system of the heart determine many of its mechanical capabilities and limitations.

Cardiac output is equal to stroke volume multiplied by heart rate.
Stroke volume is determined by preload, afterload and contractility.

Preload

The amount of blood in the LV immediately before contraction begins.

Afterload

The resistance the LV has to overcome for there to be forward flow.

Contractility

“The springiness of the spring” without the interrelated loading conditions.

Diastolic function

The ability of the LV to fill at a normal filling pressure.

Echocardiography

Echocardiography is image formation using medical ultrasound. Sound beams are emitted and reflect off tissue. The strength of the returning sound wave is then depicted as a dot on a screen. Using a large number of beams, two- or 3D picture can be built up.
Pulsed wave, continuous wave and tissue Doppler use the principle first described by Doppler, that waves reflected off a moving object can be used to calculate the speed of the object.

Myocardial fiber arrangement

The LV wall is 10 mm thick and consist of three layers: Deep sinospiral, superficial sinospiral, and the superficial bulbospiral.
These muscle fibers follow perpendicular, oblique, and helical routes from the base to the apex in a figure of eight format.
This causes twisting and untwisting during contraction and relaxation and movement from the base to the apex. (1)
The papillary muscles are an outpouching of sub-endocardial myocardium and provide chordae tendineae to both anterior and posterior mitral valve leaflets.
The Purkinje network is located in the inner one third of the wall.

Blood supply

Blood flow to the LV occurs during diastole.
The LAD and branches (septal perforators and diagonals) supply the anterior part of the septum and anterior part of the LV.
The circumflex and obtuse marginals (OM) supply the lateral wall.
The right coronary supplies the posterior part of the septum and the inferior /posterior part of the LV.
If the posterior descending artery (PDA) is supplied by the right coronary the circulation is said to be right dominant (80 % of people) (2)

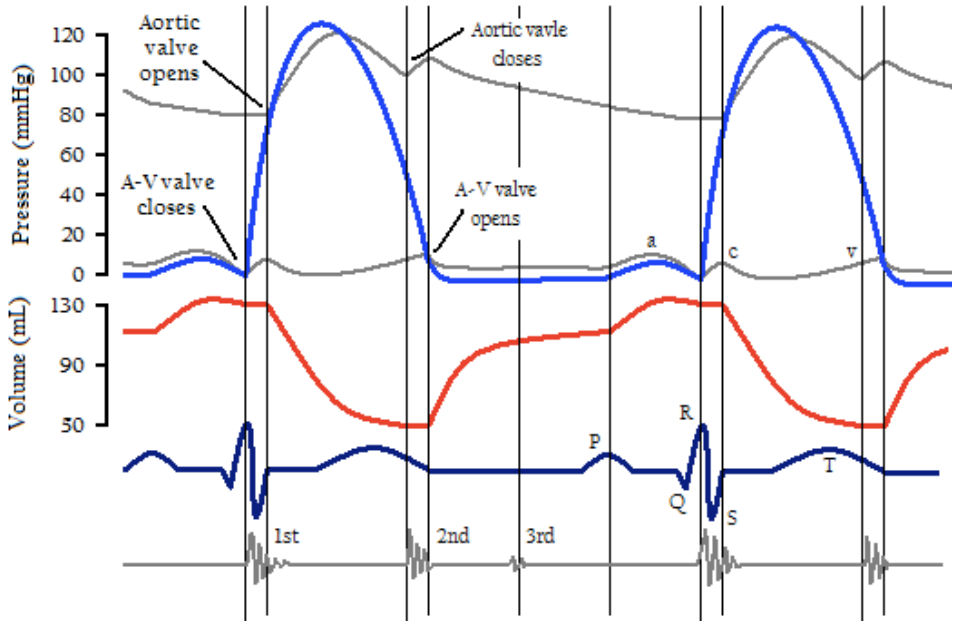
Laplace's law

The muscle generates tension and shortens during contraction and lengthens during relaxation. (3)

σ = Pr/2h
σ = Wall Tension
P = Pressure
r = Radius
h = Wall thickness
This indicates that wall stress varies directly with internal pressure and radius, and inversely with wall thickness.

The cardiac cycle

The cardiac cycle describes the electrical, mechanical, and valvular events lasting 0.8 second at a HR of 75 beats/min.
Closure of the mitral valves occurs when the LV pressures exceed atrial pressure and gives rise to the first heart sound (S1).
LV systole is divided into isovolumic contraction, rapid ejection, and slower ejection phases. LV isovolumic contraction is the time interval between mitral valve closure and aortic valve opening during which LV volume remains constant.

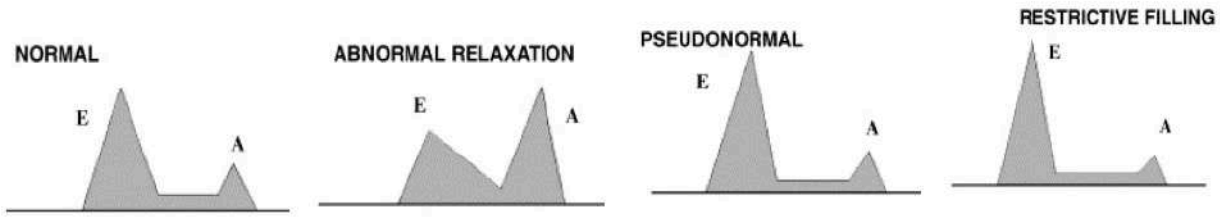


Contraction results in base to apex shortening and wall thickening.
The maximum rate of increase of LV pressure (dP/dtmax) occurs during LV isovolumic contraction and is used to estimate myocardial contractility in vivo.
The pressures in the aortic root declines to its minimum value immediately before opening.
Rapid ejection occurs when LV pressures exceed aortic arterial pressures. Two thirds of the end-diastolic volume is ejected during this rapid-ejection phase.
Dilation of the elastic aorta occurs with this rapid increase in volume as the kinetic energy is transferred to the aorta as potential energy.

This energy is subsequently released during diastole. Further ejection of blood from the LV declines as the pressures within the aorta reaches its maximum values.
As the period of slower ejection comes to an end, aortic artery pressures briefly exceed LV pressure, causing the valve to close.
This is the origin of the second heart sound (S2).
The aortic valve closes slightly before the pulmonic valve during inspiration causing splitting of S2.

The normal end-diastolic and end-systolic volumes (EDV and ESV) are approximately 120 and 40 mL therefore the SV (the difference between EDV and ESV) is 80 mL and EF (the ratio of SV to EDV) is 67%. (4)

LV diastole is divided into isovolumic relaxation, early ventricular filling, diastasis, and atrial systole. Using pulse wave Doppler at the mitral leaflets tips, this corresponds with the E wave and A wave. E/A reversal signals diastolic dysfunction. The downward slope of the A wave (decremental time; DT) signals further decline in ventricular function, as the ventricle stiffens (becomes less compliant).

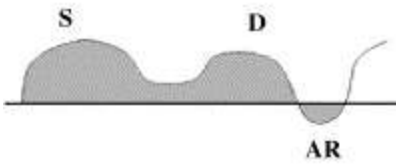


E/A	1 - 2	< 1	1 - 2	> 2
DT	140 - 240	> 240	140 - 240	< 140

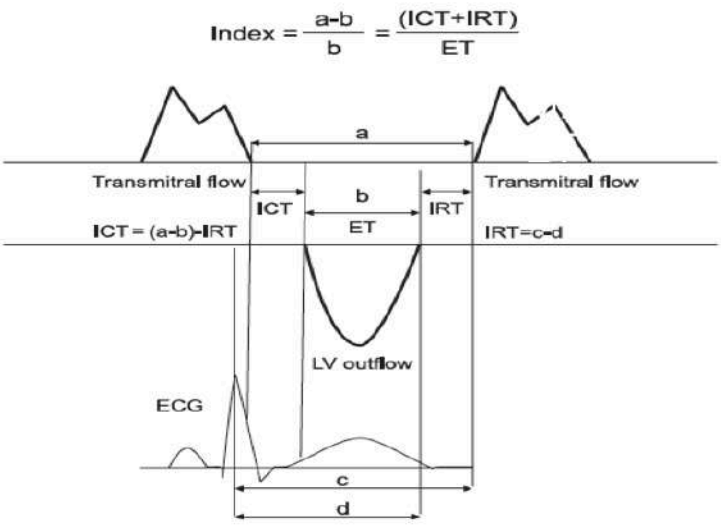
LV isovolumic relaxation is the period between aortic valve closure and mitral valve opening during which time LV volume remains unchanged. LV pressure rapidly declines as the ventricle relaxes. When LV pressure is less than LA pressure, the mitral valve opens. LV pressure continues to decline after the mitral valve opens.

This is rapid early LV filling. This contributes to 70% of the SV. There is a decline in flow causing diastasis. Blood from the pulmonary veins still deliver blood to the LA and therefore the LA now acts as a conduit. This adds another 5% to SV. Next the LA contracts adding the last 25% of SV.
The mitral valve closes and the LA now acts as a reservoir.

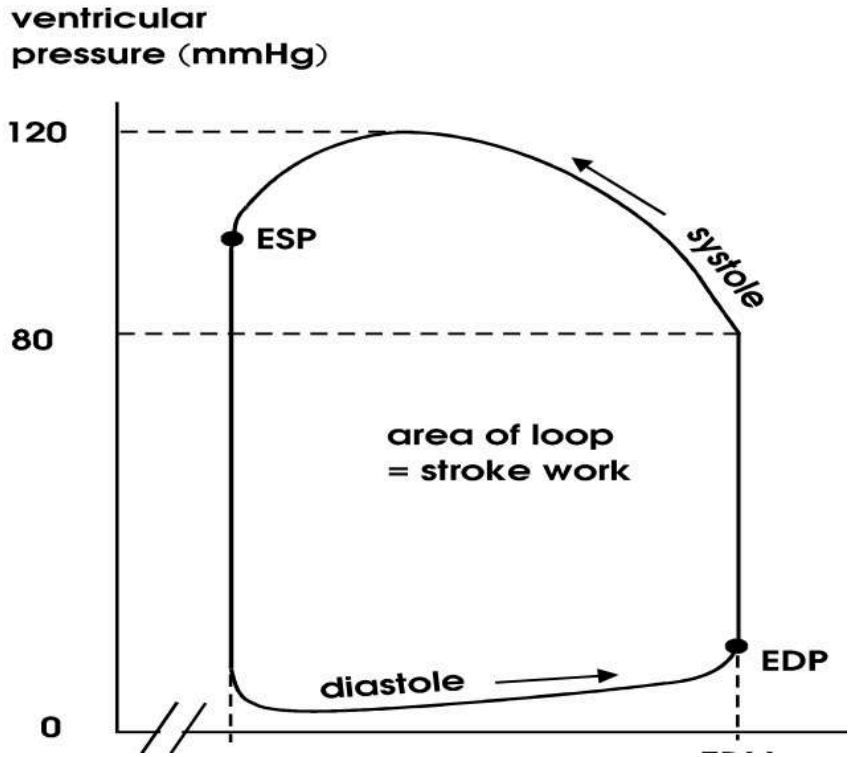
Placing pulse wave Doppler in the pulmonary veins an ASD wave pattern is obtained. The A wave corresponds with atrial contraction where some blood flows back into the veins, followed by closure of the MV and filling of the LA during ventricular systole.



The myocardial index is the ratio of the Isovolaemic contraction plus Isovolaemic relaxation to the time taken to eject blood. When the heart takes a long time in IVC and IVR and a short time to eject, there is progressive damage.



Pressure -Volume loops



ESV EDV

A plot of LV pressure to volume during a single cardiac cycle.
The plot starts at end diastole where there is an abrupt increase in LV pressure at constant LV volume. (IVC)
Opening of the aortic valve leads to ejection of stroke volume.
LV volume decreases rapidly.
When LV pressure is below aortic pressure, the aortic valve closes.
Then follows a rapid decline in LV pressure (isovolumic relaxation).
The mitral valve opens, LV filling starts and LV volume increases.

The LV pressure volume diagram is completed as the LV refills.
The area of the diagram defines the LV pressure volume (stroke) work (kinetic energy) for a single cardiac cycle.
Changes in LV loading conditions can be used to generate a series of diagrams.

Cardiac output

CO = HR x SV
EF % = (EDV-ESV) / EDV x 100
SV is affected by preload and the external resistance to emptying (afterload) and contractility.

Preload

Preload is the volume of blood in the LV at end diastole.
LV preload is affected by:

- Volume load
- Pulmonary venous blood flow
- LA function
- Mitral valve integrity
- LV compliance
- Increased pericardial pressure
- Heart rate
- AV conduction abnormality
- Atrial Fibrillation (5)
- Preload can be measured using the Simpson's disc summation method or 3D Echo.

Afterload

Afterload is the load to which cardiac muscle is subjected after the onset of contraction.
Afterload is affected by:

- Aortic impedance
- Total arterial compliance
- Total arterial resistance
- End-systolic pressure
- End-systolic wall stress
- Systemic vascular resistance
- Volume and physical properties (viscosity and density) of blood

Contractility

Contractility is affected by:

- Pressure-volume relations
- Isovolumic contraction

Studies by Frank and Starling defined the relation between LV pump performance and preload. Increase the preload and contractility increases to a point. If preload is too high CO starts to fall Contractility therefore is difficult to nail down.

Using Speckle tracking in echocardiography, strain and strain rate can be measured independently from loading conditions.

Fractional shortening

(FS) and fractional area change, are often calculated as surrogate measures of cardiac output.
FS = EDd − ESd/EDd (End-diastolic and end-systolic diameters)

Fractional area change

(FAC) may be determined using the same short-axis images by tracing the endocardial borders at end-systole and end-diastole. Most often a trained eye can see a difference of 5% say of an EF of 50 - 55%.

Isovolumic Indices of Contractility

The maximum rate of increase of LV pressure (dP/dtmax) is a derived index of global LV contractile state during isovolumic contraction as is measured in the cath lab.
LV dP/dtmax may be estimated using Echo in patients by analysis of the continuous wave Doppler mitral regurgitation waveform.

Tissue Doppler Imaging

Interrogation of septal and lateral mitral annular wall motion using low velocity Doppler.
The tissue Doppler waveform demonstrates peak velocities associated with early LV filling and LA systole (e′ and a′). The movement is due to volume change.
Trans-mitral E velocity is due to a pressure change.
E/e′ therefore is a surrogate for Pressure /volume relationship i.e. large pressure needed for small volume change is indicative a poor ventricle whereas a small pressure change resulting in a large volume change is indicative of a good ventricle.
E/e'= 8 normal,
E/e′=15 abnormal failing heart

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Notes

Heart failure therapy

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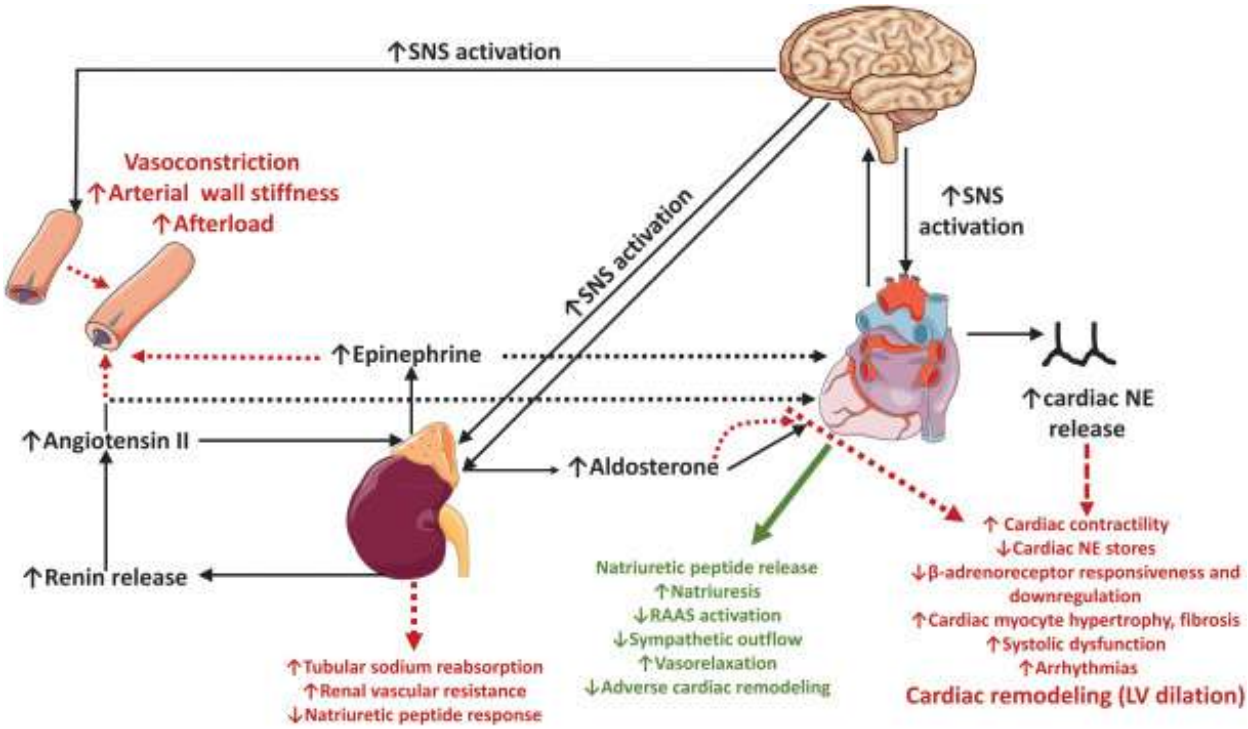
Heart failure (HF) affects an estimated 64.3 million people globally and has a very poor prognosis without therapy. The therapeutic approaches to HF are determined by the presentation as either, HF with reduced ejection fraction (HFrEF, left ventricular ejection fraction (LVEF) <40%) or HF with preserved ejection fraction (HFpEF; LVEF ≥50% and signs of diastolic dysfunction). A third type called HF with mid-range ejection fraction (HFmrEF; LVEF 40%–49% and signs of diastolic dysfunction) is used to define the diagnostic grey area between HFpEF and HFrEF.

Pathophysiology of heart failure

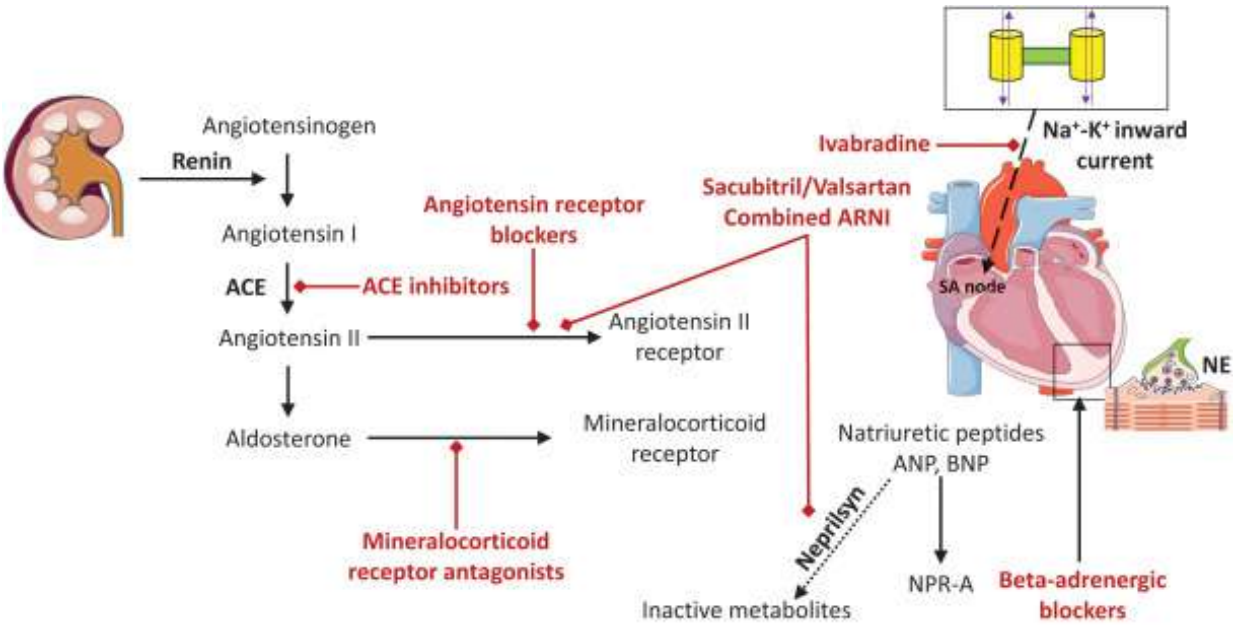
All HF types have in common a reduction in stroke volume and cardiac output. This in turn, precipitates changes in cardiac function, vascular function, blood volume, and neuro-humoral status. These compensatory mechanisms help to maintain cardiac output.

Reduction in stroke volume is due to systolic dysfunction and/or diastolic dysfunction. Loss of contractility results in systolic dysfunction and diastolic dysfunction is due to reduced ventricular compliance and impaired ventricular filling. To maintain blood pressure, there is an increase in blood volume (preload) and increase in systemic vascular resistance (afterload). Over time, these changes lead to a vicious cycle of fluid overload, increased afterload and further ventricular strain leading to further loss of contractility.



Emerging Technologies for Heart Diseases, Chapter 18 - Novel pharmacotherapies for heart failure, IN Rajapreyar, AJ Lenneman, SD Prabhu, 2020, Pages 359-380

Therapeutic interventions to improve cardiac function in HF include the use of drugs to improve contractility, vasodilator drugs that reduce ventricular afterload, and drugs to reduce fluid overload.



Emerging Technologies for Heart Diseases, Chapter 18 - Novel pharmacotherapies for heart failure, IN Rajapreyar, AJ Lenneman, SD Prabhu, 2020, Pages 359-380

The basic treatment approach for HFrEF is neurohormonal inhibition by means of angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB), mineralocorticoid receptor antagonists (MRAs), and beta-blockers. Treatment in HFpEF is symptom improvement (oedema, dyspnoea) since no drug therapy has been shown to reduce mortality in these patients. Diuretics are most commonly prescribed in HFpEF as well adequate treatment of comorbidities like hypertension and ischaemic heart disease.

Angiotensin converting enzyme inhibitors (ACEI)

Mechanism of action:

The renin-angiotensin-aldosterone system (RAAS) is involved in fluid and blood pressure regulation. The juxtaglomerular cells adjacent to the afferent arteriole produce prorenin which is cleaved to renin, an enzyme that converts angiotensinogen from the liver, to angiotensin I. Angiotensin-converting enzyme (ACE) then converts angiotensin I to angiotensin II. Angiotensin II has wide-ranging cardiovascular effects. It has the direct effect of causing vasoconstriction of precapillary arterioles and hypertrophy of both vascular smooth muscle cells and cardiac myocytes. It increases circulating levels of catecholamines by inhibiting the reuptake of noradrenaline and stimulating the release of catecholamines from the adrenal medulla. It also triggers release of hormones such as aldosterone and anti-diuretic hormone (ADH) from the adrenal cortex and pituitary. Aldosterone induces sodium reabsorption and, in turn, water reabsorption. ADH increases the synthesis of aquaporin-2 channels in the collecting duct leading to reabsorption of water.

ACEI are competitive inhibitors of ACE and prevent the conversion of angiotensin I to angiotensin II. Decrease in angiotensin II enhances natriuresis, lowers blood pressure, and prevents remodelling of smooth muscle and cardiac myocytes. Lowered arterial and venous pressure reduces preload and afterload.

Classification of ACE inhibitors according to chemical structure:

1. Sulfhydryl-containing ACE inhibitor, e.g. Captopril
2. Dicarboxylic-containing ACE inhibitors, e.g. Enalapril, Lisinopril
3. Phosphorus-containing ACE inhibitor, e.g. Fosinopril

All ACEI are prescribed orally, although enalapril can also be given intravenously. Most ACEI are prodrugs and require activation in the liver, except Lisinopril and Captopril. ACEI have similar antihypertensive effects at equivalent doses but captopril, a short-acting agent, is different and more likely to induce side effects. It is the only ACEI to penetrate the blood-brain barrier and can cause

confusion and lethargy. Patients on ACEI need regular monitoring of renal function and electrolytes for increasing potassium levels, reduction in glomerular filtration rate (GFR) or increasing creatinine levels. The dosage of ACEI will then need to be adjusted accordingly or discontinued.

Adverse effects:

Most common:

- Dry Cough (10% to 20%)
- Dizziness (12% to 19%)
- Hypotension (7% to 11%)
- Increased urea and creatinine (2% to 11%)
- Syncope (5% to 7%)
- Hyperkalaemia (2% to 6%)

Dry cough has been reported from one week, to six months, to sometimes one year after initiation of therapy. Discontinuing therapy usually resolves the cough within 1 to 4 days after but in some patients this can take up to a month. The discomfort from dry cough can affect adherence to therapy. There is also a concern that these patients have an increased propensity to develop bronchospasm. The cause has been linked to an increase in bradykinin which causes bronchial irritation, since ACE metabolises bradykinin and ACEI would then increase bradykinin levels. Alternative therapy is usually with angiotensin receptor blockers (ARB). Angioedema is a rare but life-threatening side effect which has also been linked to increased bradykinin caused by ACEI.

Hypotension can occur in patients with increased baseline concentrations of renin. These episodes can be minimised by stopping concomitantly prescribed diuretics and allowing fluid repletion. A slight reduction of GFR is common when initiating ACEI and this can be problematic in patients with already reduced GFR. Hyperkalaemia from ACEI is due to reduction in aldosterone levels which usually facilitates potassium excretion.

Contraindications:

ACEI are not recommended in pregnant patients due to teratogenic effects such as skull and lung hypoplasia, hypotension, anuria, renal failure, skeletal deformations, oligohydramnios, and death.

Relative Contraindications:

- In patients with abnormal but stable renal function therapy can be initiated under close monitoring, and discontinued if renal function starts to decline.
- Patients with aortic valve stenosis might have severe hypotension due to the reduction in afterload.
- Dehydration or hypovolaemia.

Angiotensin II receptor blockers (ARB)

Mechanism of action:

Angiotensin II is a vasoactive peptide and acts on two receptors, AT1 and AT2. AT1 activation leads to increase in sympathetic activity, vascular smooth muscle contraction with increase in systemic vascular resistance, thus blood pressure. There is also increased sodium and water retention due to increased sodium reabsorption in the proximal convoluted tubule which is enhanced by aldosterone. Chronic elevation of ATII levels causes smooth muscle and myocardial hypertrophy, endothelial dysfunction and platelet aggregation. The binding of ATII to AT2 receptors provides a modulating effect resulting in vasodilatation due to production of nitrous oxide and bradykinin, renal sodium excretion and anti-proliferative effects.

ARBs are used for the same indications as ACEIs and as an alternative for patients with ACEI-induced cough and angioedema. All ARB's are highly protein-bound (>85%). Bioavailability varies widely from 23% for valsartan to 60% to 80% for irbesartan. Most are dosed once daily, except losartan and eprosartan which have short half-lives and may require twice daily dosage. Eprosartan and candesartan are eliminated primarily via the kidney and dosage will need to be adjusted in patients with renal impairment.

Adverse effects:
ARBs are generally well tolerated and have a low incidence of side effects. The incidence of angioedema and cough is rare with ARB although case reports do exist. Hypotension and/or renal failure can occur when blood pressure or renal function is highly dependent on RAAS, e.g. in patients with bilateral renal artery stenosis or heart failure with hypotension, where these drugs are contraindicated.

Contraindications:
ARBs are contraindicated in pregnant patients due to the harmful effects on the fetus described under ACEI therapy. ARBs can cause hyperkalemia in patients with renal disease or in combination with drugs likely to cause hyperkalemia (K+ supplements, K+ sparing diuretics, ACEI, non-steroidal anti-inflammatory agents). The blood pressure-lowering effect of other antihypertensive drugs is potentiated with the use of ARBs and may require dose adjustment. The use of ARBs with ACEI should be avoided, due to a higher incidence of hypotension, acute renal failure, or hyperkalemia with no additional survival benefit in clinical trials.

Direct renin inhibitor, aliskiren, will not be discussed in this chapter since no value has been found using this drug in HFrEF and more adverse drug-related events were reported in clinical trials.

Mineralocorticoid receptor antagonists (MRAs)

Mechanism of action:
Mineralocorticoid receptors (MR) are steroid hormone receptors in the subfamily of nuclear receptors. These receptors act as intracellular receptors and nuclear transcription factors. This subfamily also consists of the androgen receptor, the glucocorticoid receptor (GR), the progesterone receptor, and oestrogen receptors. The MR has the same binding affinity for aldosterone and cortisol and mediates fluid, electrolyte, and haemodynamic homeostasis, as well as tissue repair.

Classification of MRAs:
1. Steroidal structure: First and second generation MRAs, spironolactone and eplerenone
2. Non-steroidal structure: Third-generation MRAs, finerenone and canrenone

Spironolactone, the first steroidal MRA, was primarily developed and used for the treatment of oedema, ascites and high blood pressure. The RALES trial, found that spironolactone substantially reduced the risk of both morbidity and death among patients with severe heart failure. Eplerenone has a higher selectivity for MR compared to spironolactone, therefore avoiding hormonal side effects such as gynaecomastia. Other side effects such as worsening of renal function and hyperkalaemia prompted the development of third-generation MRAs, such as finerenone and canrenone, which are nonsteroidal.

Spironolactone is a nonselective competitive antagonist of the aldosterone receptor. Administration also results in antagonism of the androgen, glucocorticoid, and progesterone receptors. Spironolactone is extensively and rapidly metabolised to active metabolites, which contribute to a major portion of the aldosterone inhibition. Although the half-life of spironolactone is 1.4 hours, the half-lives of the metabolites range from 14 to 22 hours.

Food increases the bioavailability of spironolactone by 100%, the clinical effect of which is unknown. Both spironolactone and canrenone are more than 90% protein bound, principally to albumin. Spironolactone is completely metabolised in the liver and the metabolites are excreted in the urine and bile. The dosage of spironolactone should be reduced in elderly patients, as increased serum concentrations of the drug have been found in this population.

Eplerenone is a selective aldosterone antagonist. Eplerenone is well absorbed following oral administration, with a bioavailability of approximately 67% and reaching a peak plasma concentration in about 1.5 hours. Food does not affect its absorption and it is approximately 50% protein bound, which is less than spironolactone and canrenone making it more potent. Eplerenone is metabolised by the cytochrome P-450 enzymes in the liver to inactive metabolites. The metabolism of eplerenone may be altered in patients with advanced age, renal impairment, hepatic impairment, or heart failure and these patients require more frequent monitoring. Eplerenone is eliminated in the urine (67%) and faeces (32%). Only 6.8% of the eliminated drug is unchanged as the parent compound. The

elimination half-life is approximately four to six hours. Eplerenone exhibits minimal activity against androgen, glucocorticoid, or progesterone receptors.

Beta-Blockers

Mechanism of action:

The beta-receptor is an adrenergic G-protein coupled receptor. There are three types of beta-receptors: beta1, beta2, and beta3. The beta-receptors are stimulated by the sympathetic nervous system with catecholamines adrenaline and noradrenaline, resulting in an increase in Ca2+ concentration through cAMP/ PKA-dependent pathway. The beta1-receptor, located mainly in the heart, induces positive chronotropic (increases heart rate) and inotropic effects (increases contractility of the myocardium). In the kidneys, beta1-receptor activation results in the release of renin. The beta2- receptor in smooth muscle cells promotes relaxation, in skeletal muscle cells and liver increases glycogenolysis. The beta3-receptor is located in adipose tissue where it induces lipolysis.

Tissue	**Receptor**	**Effect**
Heart	α1	Positive and negative effects on contractility
SA node	β1, β2	Increase in heart rate
AV node	β1, β2	Increase in conduction velocity
Atria	β1, β2	Increase in contractility
Ventricles	β1, β2	Increase in contractility, conduction velocity and automaticity of idioventricular pacemakers
Vascular smooth muscle	α1, α2	Vasoconstriction
	β2	Vasodilatation
Skeletal muscle	β2	Vasodilatation, increased contractility, glycogenolysis, uptake of K^+
Liver	α1	Glycogenolysis and gluconeogenesis
	β2	Glycogenolysis and gluconeogenesis
Pancreas (β cells)	β2	Promotes insulin and glucagon secretion
	α2	Inhibits insulin secretion
Fat cells	β1	Lipolysis
Bronchi	β2	Bronchodilation
Kidneys	β1	Renin release
Gallbladder and ducts	β2	Relaxation

Frishman, W. H. (2007), A Historical Perspective on the Development of β-Adrenergic Blockers. The Journal of Clinical Hypertension, 9: 19–27.

Stimulation of beta1-receptors can also lead to adverse remodelling, interstitial fibrosis and arrhythmia provocation in the heart. Inhibition of adrenergic activity with the use of beta-blockers is associated with attenuation of all these effects. Beta-blockers are classified as non-selective beta-blockers or selective beta-blockers (for one of the three subtypes of beta-receptors). Beta-blockers may be administered both intravenously and orally.

Classification of beta-blockers:

- The first-generation non-selective beta-blockers (e.g. propanolol).
- The second-generation selective beta1-blockers (e.g. metoprolol, bisoprolol, atenolol, and esmolol).
- The third-generation beta-blockers with combined alpha-blocking and non-selective beta-blocking (e.g. carvedilol)

Beta-blockers used to be contraindicated in patients with heart failure, but selective beta1-blockers or non-selective combined alpha- and beta-blockers are now a part of the standard treatment of heart failure since a number of trials showed beneficial effects. These trials suggest that adding beta-blockers to conventional treatment may result in an approximately 24% to 35% relative risk reduction in mortality, may improve heart failure symptoms, and may reduce the risk of heart failure hospitalisations regardless of age and sex.

Possible benefits include:
1. Mitigation of cardiotoxic effects of catecholamines.
2. Antihypertensive effect through inhibition of renin, angiotensin II, and noradrenaline.
3. Anti-ischaemic effect through reduction in myocardial oxygen demand by decreasing heart rate, cardiac contractility and systolic blood pressure. Reduction in heart rate prolongs diastolic filling and coronary diastolic perfusion time.
4. Reduction in renin, angiotensin II and aldosterone by blockade of β-adrenoceptors on renal juxtaglomerular cells.
5. Improvement in left ventricular structure and function by reducing ventricular size and increase ejection fraction leading to a reverse of cardiac remodelling

Adverse effects:
These are both cardiac (hypotension, bradycardia/heart block) and non-cardiac (fatigue, masking of symptoms of hypoglycaemia) adverse effects. Historically, beta-blockers were contraindicated in patients with chronic obstructive pulmonary disease (COPD). However, cardio-selective beta-blockers have been shown to reduce mortality and COPD exacerbations even in COPD patients without cardiovascular disease. Beta- blockers induce upregulation of beta-adrenergic receptors, resulting in catecholamine sensitivity. Abrupt beta-blocker withdrawal can cause arrhythmias (e.g. ‘catecholamine storm’ leading to refractory ventricular tachycardia) and angina.

Cautions:
- Asthma (seek specialist advice)
- COPD
- Peripheral vascular disease

Absolute contraindications:
- Significant bradycardia (<50 beats/min)
- Mobitz type II or complete heart block
- Acute decompensation of HF

Common drug interactions:
- Verapamil/diltiazem (contraindicated with a beta-blockers, and also in HFrEF generally)
- Digoxin/amiodarone

Angiotensin receptor-neprilysin inhibitor (ARNI)

The natriuretic peptides are a group of vasoactive peptides which are released in response to elevated cardiac filling pressures, sodium and water retention, activation of the RAAS and the sympathetic nervous system. They counteract the increase in intra-cardiac volume/pressure through their natriuretic and diuretic properties. Further beneficial effects include vasodilation and mitigation of cardiac fibrosis and hypertrophy. NPs hypothetically presented a potential therapeutic target in HF management.

However, clinical trials did not show that administration of exogenous NPs reduced mortality or HF hospitalisation in patients with HFrEF. An alternative approach was to block neprilysin, a membrane-bound endopeptidase found predominately in the kidney. A-, B-, and C-type natriuretic peptides (ANP, BNP, CNP) and urodilatin are hydrolysed by neprilysin, therefore, inhibition of neprilysin activity may result in elevated levels and activity of NPs.

Unfortunately, as a single agent, neprilysin does not have a sustained anti-hypertensive effect. A possible solution was a combination of neprilysin with ACEI, however this led to increased risk of angio-oedema and did not reduce all-cause mortality or HF hospitalisation in clinical trials. Subsequently, a combination of neprilysin and ARB was developed, sacubitril/valsartan. The risk of

angio-oedema was thought to be lower with this combination due to the blockade of the angiotensin II type 1 receptor as opposed to ACE inhibition. Additionally, the active metabolite of sacubitril, sacubitrilat, does not inhibit aminopeptidase P. This enzyme, involved in bradykinin breakdown, was discovered to be inhibited by ACEI, helping explain the unexpected excess risk of angio-oedema.

The combination of valsartan/sacubitril was evaluated against enalapril in the PARADIGM-HF study in outpatients with HFrEF on optimal medical therapy. The trial was stopped early because of benefit shown in the treatment arm. Valsartan/sacubitril was superior to enalapril in terms of all-cause mortality, cardiovascular mortality and fewer hospitalisations for worsening heart failure.

The concomitant use of ARB or direct renin inhibitor is contraindicated with sacubitril/valsartan due to the risk of hyperkalaemia and renal dysfunction. ACE inhibitors are contraindicated due to the additional risk of angio-oedema. Any patient prescribed an ACE inhibitor should have a minimum 36 h washout period after discontinuation before switching to sacubitril/valsartan. Patients must be monitored for renal dysfunction and hyperkalaemia. Blood pressure must be monitored and the medication should be avoided in patients with a systolic blood pressure of less than 100 mmHg. If a patient develops angio-oedema the medication must be stopped immediately.

Ivabradine

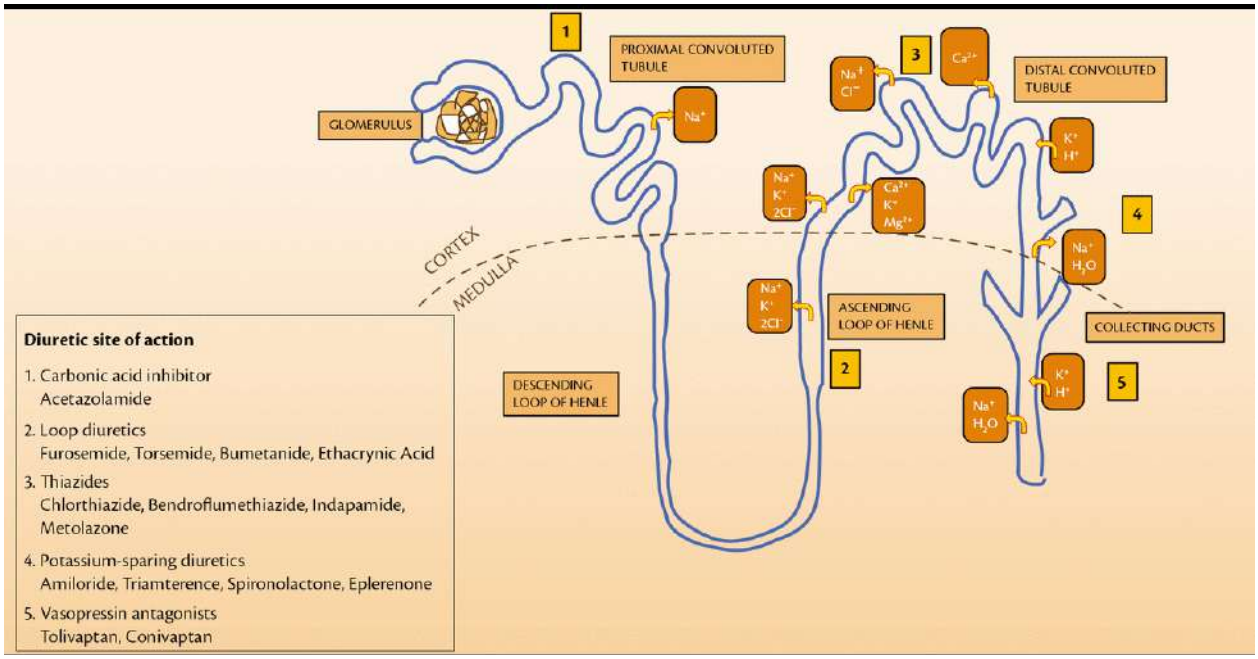
Ivabradine selectively blocks 'funny current' (I_f) channels in the pacemaker cells of the sinoatrial node thus slowing down the heart rate. Binding of the drug reduces the Na and K flow through this channel and flattens the spontaneous depolarisation slope of the pacemaker cells and therefore lowers heart rate. The faster the initial heart rate the greater the degree of heart rate reduction with ivabradine. There is no effect on myocardial contractility or relaxation, on atrioventricular or intraventricular conduction, or on the vasculature.

Ivabradine was first used in ischaemic heart disease with poor left ventricular function. In the SHIFT trial, ivabradine was evaluated in heart failure and showed a significant reduction in cardiovascular mortality and heart failure hospitalisation. It was well tolerated and although symptomatic and asymptomatic bradycardias were reported (in about 5% of patients) less than 1% had discontinuation of treatment. No pro-arrhythmic effects were observed and atrial fibrillation was uncommon. Visual side effects (blurring vision or flashes) due to blockade of I_f channels in the retina, were also uncommon. Results suggest that ivabradine in addition to beta-blocker therapy is safe in patients with chronic heart failure and low ejection fraction. In terms of further cardiovascular effects, ivabradine does not alter blood pressure, but does increase the force–frequency relationship which is helpful in heart failure. In the normal heart, force increases with the increase in heart rate (positive force/frequency relationship), whereas in the failing left ventricle, increased heart rate is associated with a decrease in force. This effect is reversed by ivabradine. Chronic remodelling is also mitigated by ivabradine.

Ivabradine is indicated for the management of symptomatic HFrEF patients, on maximal therapy, in sinus rhythm, heart rate ≥75 b/mim in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated. Due to its mechanism of action, the drug is inactive in patients with permanent atrial fibrillation and in pacemaker-dependent patients.

Contraindications include sick sinus syndrome, pacemaker-dependent patients, patients on verapamil or diltiazem, cytochrome P450 enzyme inhibitors and high/third-degree AV block.

Diuretics



HFrEF pharmacological treatment: diuretics Author(s): Rhondalyn Forde-McLean and Mariell Jessup, ESC CardioMed

Loop diuretics

The loop diuretics are the mainstay in treatment of HFrEF. These diuretics inhibit the Na-K-Cl transporter in the ascending limb of the loop of Henle, thus blocking reabsorption of sodium. This overwhelms the reabsorption capacity sodium transporters in the distal convoluted tubule leading to sodium and water excretion. Loop diuretics are used in all types of heart failure especially in severe or refractory HFrE. Furosemide is the most widely used and least expensive of the loop diuretics, but oral torsemide and bumetanide have better bioavailability, which helps in severe heart failure where bowel oedema can affect drug absorption. Intravenous furosemide is twice as potent as its oral milligram equivalent. In patients in acute decompensated heart failure there is no significant difference in using high-dose compared to a low-dose furosemide, and no difference in intravenous bolus administration compared continuous intravenous infusion (The DOSE trial). This study also showed no increase in creatinine for the different treatment strategies. The common metabolic derangement is hypokalaemia which can predispose to lethal arrhythmias. Unlike other diuretics, loop diuretics will be effective even when the intravascular volume has normalised, leading to a risk of dehydration, hypotension, and acute kidney injury. Ototoxicity which is generally reversible, is a class-related side effect of the loop diuretics, and more likely with ethacrynic acid or high doses of furosemide.

Thiazide and thiazide-like diuretics

The thiazide diuretics are widely used for the treatment of hypertension and peripheral oedema. Their mechanism of action is to inhibit sodium and water reabsorption in the distal convoluted tubule by acting on the sodium ion transport. Most filtered sodium is reabsorbed prior to reaching the distal convoluted tubule, thus these drugs are only moderately effective and are prescribed in mild to moderate heart failure when the estimated glomerular filtration rate is >50% of normal. The exception, metolazone, may be used in patients with a creatinine clearance of less than 30 mL/min. In severe HFrEF, thiazides can be used in addition to loop diuretics to enhance diuresis. Bendroflumethiazide and hydrochlorothiazide have good oral bioavailability. The major side effects are: hyponatraemia, as there is little free water clearance, and increase in calcium and uric acid levels. The combination of quinidine and thiazide diuretics can lead to the development of torsade de pointes which is exacerbated by hypokalaemia.

Potassium-sparing diuretics

Amiloride and triamterene act directly on the distal convoluted tubule and collecting duct, inhibiting sodium channels. There is a modest increase in sodium excretion; therefore, these drugs are usually combined with a loop or thiazide diuretic. The major side effect is hyperkalaemia, which can be life-threatening and they are to be avoided in patients with baseline hyperkalaemia.

Mineralocorticoid antagonists

Spironolactone and eplerenone also inhibit sodium reabsorption in the distal convoluted tubule. They work through competitive inhibition of aldosterone-dependent potassium channels; therefore their effectiveness is altered by the levels of aldosterone secretion. When aldosterone receptor antagonists are used with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, there is a greater risk of hyperkalaemia. Large doses of spironolactone are often utilized in patients with oedema and cirrhosis, and this makes this specific patient population at a dose-related risk of metabolic acidosis.

Carbonic anhydrase inhibitors

Acetazolamide is a potent carbonic anhydrase receptor inhibitor in the proximal convoluted tubule of the nephron. This leads to increased excretion of HCO_3-, Na, and K in the proximal tubule and may cause metabolic acidosis, limiting the use of this agent. Acetazolamide can be useful in a scenario where contraction alkalosis has developed due to excessive diuresis with another agent. Other toxic effects include bone marrow suppression and skin lesions.

Vasopressin antagonists (tolvaptan, conivaptan)

In heart failure, there are elevated levels of arginine vasopressin promoting reabsorption of water to increase blood volume. Vasopressin antagonists block the V_2-receptors in the renal collecting duct and the V_{1a}-receptors in the vasculature leading to a reduction in afterload. Clinical trials done with this class of drugs have shown no improvement in clinical outcomes, therefore the only place in treatment is in hypervolaemic and euvolaemic hyponatraemia when other strategies have failed.

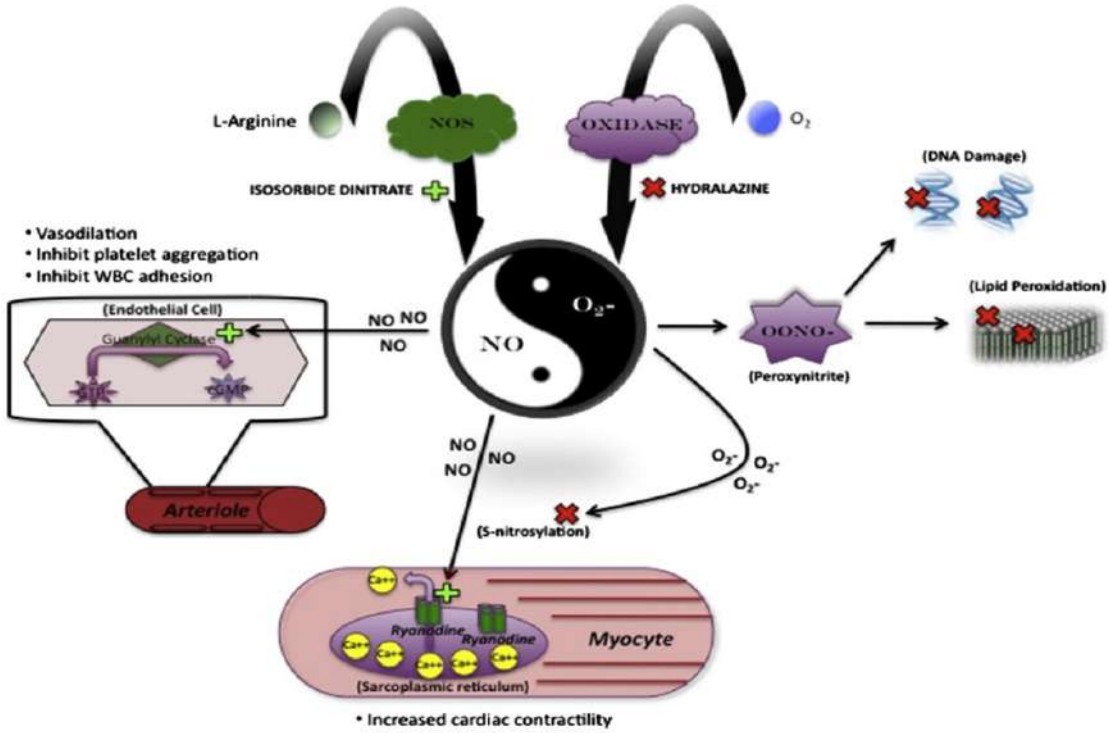
Diuretics are associated with a decrease in biventricular filling pressures and improved quality of life, but long-term studies have not shown a mortality benefit with diuretic therapy. A potential explanation is that a reduction in circulating volume from diuretic therapy may cause a reflex stimulation of the renin/angiotensin axis and activation of the sympathetic nervous system. For this reason, in patients with HFrEF, diuretics should always be used in combination neuro-hormonal blockade therapies.

As a part of overall HFrEF management, patients with HFrEF should be counselled about dietary restrictions, fluid management, and the effects of climate and concomitant medications that may influence volume status. In symptomatic HFrEF it is recommended that sodium is restricted to less than 2 g of sodium daily, (little data to support this recommendation) and fluid restriction of below 2 L daily in patients who are symptomatic despite maximum therapy. HFrEF patients should also be instructed to avoid non-steroidal anti-inflammatory drugs which can increase the risk of renal failure in patients with chronic renal insufficiency, on ACEI/ARB/diuretics. Follow up and monitoring for electrolyte derangements, hyperuricaemia, hypovolaemia, and renal impairment, which are not uncommon side effects, is important.

Hydralazine and nitrates

Nitric oxide (NO) and reactive oxygen species (ROS) both participate in signalling pathways and are delicately balanced to maintain cardiovascular homeostasis. This interaction, called the “nitroso-redox balance”, occurs within cells and affects enzyme production, chemical reactions, and post-translational modification of effector proteins. Disruption of this equilibrium has potential hazardous consequences affecting diverse cellular components. In heart failure, the imbalance between nitric oxide production and oxidative stress induced by reactive oxygen species affects endothelial function, peripheral vasomotor tone, cardiac myocyte contractility, and cell death.

NO is produced by nitric oxide synthase from L-arginine. NO mediates signalling through two mechanisms: via guanosine cyclase in the cyclic guanosine monophosphate pathway in medium-to-large sized vessels to produce smooth muscle relation, and by post-translation modification of effector molecules, specifically S-nitrosylation which affects myocardial contractility. Superoxide, one of the ROS, is generated from oxygen by oxidases. Superoxide regulates S-nitrosylation at physiological levels, but at excess levels, it can prevent S-nitrosylation and directly convert nitric oxide into cytotoxic molecules, such as peroxynitrate.



Current perspectives on hydralazine and nitrate therapies in heart failure. Cole RT, Gupta D, Butler J. Heart Fail Clin. 2014 Oct;10(4):565-76.

In heart failure, the hypothesis is that, superoxide production is increased, disrupting nitric oxide synthesis which interrupts effector signalling and causes cellular dysfunction. Isosorbide dinitrate, a drug that stimulates the nitric oxide pathway, and hydralazine, an antioxidant that inhibits superoxide synthesis, may restore the balance of nitric oxide and superoxide production in the heart and peripheral circulation.

However, despite studies showing beneficial effects on both hospitalisation for heart failure, and mortality in black African patients, this therapeutic combination is underused. This therapy can be used in patients who are unable to tolerate a RAAS inhibitor, or who remain symptomatic despite receiving therapy with a BB, RAAS inhibitor and MRA.

Digoxin

Digoxin is a cardiac glycoside. It inhibits the sodium–potassium adenosine triphosphatase pump (Na/K-ATPase) on the extracellular side of the myocyte leading to an increase in intracellular sodium concentration. The rise in intracellular sodium slows the activity of the sodium–calcium exchanger that leads to a rise in intracellular calcium. This calcium is stored in the sarcoplasmic reticulum and released during depolarisation, increasing cardiac myocyte contractile force.

Digoxin increases vagal tone which slows down the sinus node and atrioventricular conduction. The slower heart rate and improved contractility is beneficial in patients with HFrEF. Digoxin may also have direct renal effects, increasing diuresis and natriuresis.

Although Na/K-ATPase is present on all cell membranes, digoxin appears to have minimal effects on skeletal and vascular smooth muscle, but greater effects on cardiac muscle, the autonomic nervous

system, and the kidney. Toxic doses of digoxin prevent cellular entry of potassium and causes malignant hyperkalaemia. Cardiac glycosides reduce cardiac myocyte resting membrane potential and in the setting of hypokalaemia, hypomagnesaemia, or hypercalcaemia, increase susceptibility to arrhythmias.

Digoxin has high oral bioavailability, relatively low plasma protein binding and a high volume of distribution. This indicates a higher concentration in tissue compared to plasma. Its distribution half-life from plasma to tissues is about 8 h and elimination half-life is about 1.5 days, if renal function is normal since it is mainly excreted unchanged by the kidney. Therefore, the value of measuring the plasma concentration of digoxin is uncertain, other than to confirm either compliance or toxicity. Analyses of plasma concentrations suggest that 0.6–1.0 nmol/L (0.5–0.8 ng/mL) may be clinically effective and doses >1.4 nmol/L (>1.1 ng/mL) are associated with an increased risk of toxicity and mortality. Steady-state plasma concentrations are reached within 2 weeks.

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Notes

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Paracetamol
Acetaminophen

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Historical perspective

Paracetamol was first synthesized by an American chemist, Harmon Morse, in 1878. It was found to be the active ingredient of the more popularly used Phenacetin. Paracetamol only became commonly used in the 1950's when Phenacetin was found to be nephrotoxic and cause methemoglobineamia. Paracetamol overtook the general use of Aspirin in the 1980's when Reye syndrome was associated with the latter.

Administration	Oral: Tablets,capsules, effervescent tablets and syrup. Rectal: Suppositories Intravenous: Perfalgan®
Oral bioavailability	80%
Therapeutic plasma concentration	10mg/L
Peak plasma levels after administration	Tablets 1-2hrs, Syrup 30 min, IV 15min after infusion completed
Elimination $t_{1/2}$	1.5-3 hrs – varies with maturity
Volume of Distribution	0.9 L/kg
Protein binding	Less than 10%
Metabolism	Hepatic, glucuronidation, sulphation, 5-10% by P450 to NAPQI
Excretion	Renal, sulphate and glucuronide metabolites

Formulations

Oral paracetamol

Very little absorption occurs through the gastric mucosa. Paracetamol has a pKa of 9.5 and is mostly absorbed in the small intestine. Bioavailability is 80% after oral administration. Co administration with caffeine increases absorption. Absorption halftime is increased in infants younger than 3 months. Medication errors are the leading cause of acute liver failure in children. The UK Medicines and Healthcare Regulatory body suggested narrower age ranges for dosing instructions and reduced the maximum daily dose from 90mg/kg to 75mg/kg.

Rectal paracetamol

Absorption is unpredictable and variable between patients. An initial loading dose of 40mg/kg is suggested followed by 20mg/kg 6 hourly. Suppositories should not be divided in half as drug spread is not uniform throughout the suppository.

Intravenous formulation

Paracetamol is not water-soluble and therefore was not available in its intravenous form until recently. Propacetamol, a prodrug of paracetamol, is more water soluble and preceded IV paracetamol. It is more allergenic and more costly than paracetamol. 2g of propacetamol is hydrolysed to an equivalent of 1g paracetamol. IV Perfalgan® was manufactured by adding hydrophilic ingredients like mannitol and disodiumphosphate. Oxidation is prevented by adding cysteien HCl in an oxygen free manufacturing process. It is available as a 10mg/ml clear solution in 50ml or 100ml bottles. The

current pharmaceutical dosage recommendation or IV Perfalgan® is 1g 6 hourly for adults; 7,5mg/kg 6 hourly in neonates and 15mg/kg 6 hourly in children. Newer research indicating a larger volume of distribution in neonates and slightly slower clearance, suggests a loading dose of 20mg/kg as in adults, but longer dosing intervals. It is suggested that premature babies younger than 31 weeks PGA should only receive paracetamol at 12 hourly intervals.

Mechanism of action

Paracetamol was initially categorized as a nonsteroidal anti-inflammatory drug (NSAID). It's mechanism of action was compared to that of classical NSAIDs, such as acetyl salicylic acid which inhibits the cyclooxygenase (COX) pathway. Paracetamol was proven to be very effective at reducing pyrexia and mild to moderate pain but it has been ineffective as an anti-inflammatory drug. It does not share the same side effect profile as NSAID's and have no effect on platelet function. The mechanism of action remained elusive for many years and current hypothesis are still not complete.

The latest hypothesis is that the enzyme responsible the metabolism of arachidonic acid to the prostanoids, known as cyclooxygenase, have 2 active sites: a cyclooxynase (COX) site and a peroxidase (POX) site. The conversion of arachidonic acid to the prostanoids is a 2 step process, with activity from COX to produce the unstable intermediate prostaglandin G2 (PGG2), which is then converted to prostaglandin H2 (PGH2) via peroxidase (POX). COX needs to be in an oxidised state for function and POX provides this oxidation. Paracetamol acts as an alternative reducing co-substrate for POX, preventing oxidation of COX, and reduce the production of PGH2. This inhibition by paracetamol is only possible under conditions of low arachidonic and peroxide levels. Central nervous system levels of arachidonic acid and peroxides are low and explain the predominantly central action of paracetamol. Once cell structure has been damaged it leads to the release of large amounts of lipid hydroperoxides which renders paracetamol ineffective under conditions of inflammation.

Another proposed mechanism of action for the analgesic properties of paracetamol is the modulation of the endogenous cannabinoid system. This mechanism may provide an explanation for the "relaxation" or "calming" effect of paracetamol. The current hypothesis is that paracetamol is de-acetylated to p-aminophenol in the liver. P-aminophenol is conjugated with arachidonic acid by fatty acid amide hydrolase (FAAH) enzymes to form N-arachidinoyl-phenolamine (AM404) in the brain, spinal cord, and dorsal root ganglia. AM404 is a weak agonist of cannabinoid receptors type 1 and 2 (CB1 and CB2), and an inhibitor of the anandamide membrane transporter (AMT), which leads to increased levels of endogenous cannabinoids. AM404 is also a potent activator of the vanilloid subtype 1 receptors (TRPV1) Paracetamol also directly activates TRPV1 receptors while cannabinoid CB1 receptors do so indirectly by increasing endogenous anandamide levels. Both mechanisms are present in thermoregulatory and pain centres in the brain.

The involvement of serotonergic pathways in the action of paracetamol have been deducted by the observation that the analgesic activity of paracetamol is reduced in the presence of 5-HT3 antagonists. There is also suspected interaction between endocannabinoid and serotonergic pathways. There has been concern that the co-administration of 5-HT3 antagonists intraoperatively to treat nausea and vomiting, would decrease the efficacy of paracetamol analgesia. This has not been shown to be of clinical significance.

Clearance

Paracetamol is metabolised in the liver by conjugation with glucuronides and sulphates to non-toxic metabolites. These metabolites are excreted renally. Sulphation predominates in neonates as the glucuronidation pathway only matures at 2 years of age. By adulthood the glucuronidation pathway predominates.

Elimination half-life decreases with maturity. 1.5-3 hrs in adults, 2.5-4 hrs in term neonates and up to 11 hrs in very premature infants. It is important to adjust the dosing interval accordingly. Clearance is not affected in the geriatric population but they could be susceptible to hepatotoxicity due to deficient glutathione stores.

Paracetamol is still the preferred choice of analgesic in patients with chronic liver failure, but dose intervals should be longer. Although alcohol abuse is mentioned as a risk factor for increased toxicity,

no proof exists for toxicity with therapeutic doses.

Hepatotoxicity

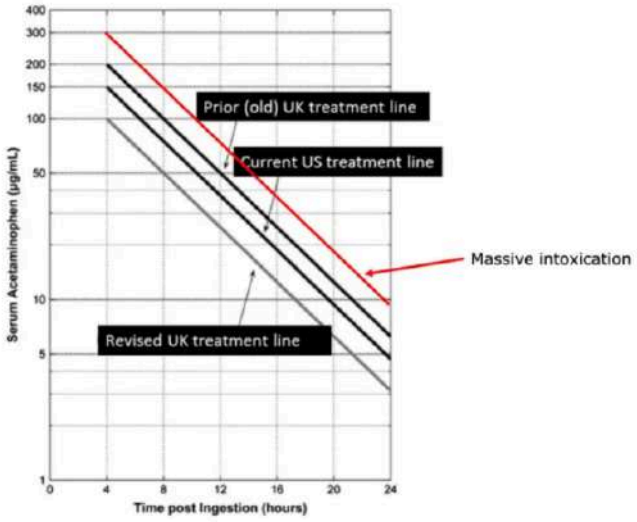
At therapeutic levels 90% of paracetamol is broken down via sulphation and glucuronidation to non-toxic metabolites. Only 5-10% of paracetamol is oxidised by CYP2E1 enzymes. This CYP450-dependant pathway is susceptible to enzyme induction and genetic variability. Oxidation by CYP2E1 leads to the formation of the toxic intermediate metabolite, N-acetyl-p-benzoquinine imine (NAPQI). NAPQI is detoxified through conjugation with glutathione and eliminated in urine and bile. When glutathione capacity is overwhelmed through overdose of paracetamol or shortage of glutathione, the metabolite, NAPQI will cause hepatotoxicity which can lead to fulminant liver failure and death. NAPQI causes direct damage by forming covalent bonds with cell proteins and indirectly by depleting glutathione capacity. Glutathione reduces levels of reactive oxygen species and peroxynitrite in the mitochondria and cell cytosol. Without glutathione, oxidative stress activates the opening of mitochondrial permeability transition pores that results in the destruction of the membrane potential and stops ATP synthesis. This results in the breakdown of DNA and cell membranes and the induction of apoptosis, resulting in cell death and acute inflammation.

Enzyme inducers such as alcohol and isoniazide increase the formation of NAPQI and increase the risk of hepatotoxicity at supratherapeutic levels of paracetamol. Neonates have immature P450 enzyme function and produce NAPQI at a slower rate.

Paracetamol overdose is treated with N-acetylcysteine (NAC). NAC is a precursor of glutathione, it increases the concentration of glutathione available for the conjugation of NAPQI. NAC also enhances sulphate conjugation of unmetabolized paracetamol and functions as an anti-inflammatory and antioxidant.

The Rumack-Matthew nomogram is used to determine the need for NAC and is a paracetamol blood concentration plotted against the time passed since ingestion. The nomogram varies slightly between countries with the UK opting for a more aggressive treatment line.

Interpretation of toxic paracetamol levels is challenging in the setting of combination preparations (opioids combined with paracetamol), slow release paracetamol preparations and staggered multiple does



Side effects

Side effects with paracetamol are very rare when therapeutic doses are used. Non-specific gastro intestinal symptoms can occur with prolonged use and rare cases of pancreatitis have been reported. Hypotension is listed as one of its side effects and is mostly noted in sick patients in the ICU setting. Paracetamol has no clinically significant effect on coagulation as is the case with NSAIDs.

Paracetamol and Asthma

Paracetamol causes bronchoconstriction in about 7% of aspirin-sensitive asthmatics. The episodes are less severe and more easily treated than if caused by aspirin. Epidemiological studies indicate that paracetamol increases risk of asthma in children and adults even after prenatal exposure. Causality is difficult to establish as there are several confounding factors. Children with recurrent upper airway or ear infection will have a higher incidence of asthma and bronchospasm, and will take paracetamol more frequently. Glutathione acts as a pulmonary anti-oxidant and depletion of glutathione by regular paracetamol use may increase pulmonary inflammation. Recent studies reveal that a strong link exist between children with a genetic variation for glutathione S-transferase Pi (GSTP) and the development of wheezing before the age of 5. It is postulated that this polymorphism leads to higher levels of NAPQI and myeloperoxidase in the airway of fetuses after maternal exposure to paracetamol.

Drug interactions

Paracetamol absorption is increased by substances that increase gastric emptying and decreased by substances that decrease gastric emptying such as anticholinergic agents and opioids. This is of importance when combination preparations are taken. Opioids are often combined with paracetamol. Cholestyramine will reduce the absorption of paracetamol. Enzyme inducers such as carbamazepine, phenytoin or barbiturates may increase the risk of toxicity. Concomitant use of paracetamol with oral anticoagulants may cause variations of INR values.

Novel uses of paracetamol

Prevention of hyperalgesia

A loading dose of paracetamol has been found to be as effective as ketamine bolus and infusion at reducing hyperalgesia following intraoperative remifentanil infusion. Potential mechanisms leading to hyperalgesia include antinociceptive tolerance and N-methyl-D-aspartate (NMDA) pain facilitation. Further studies are needed to confirm results and the mechanism by which paracetamol reduces hyperalgesia is still unclear.

Enhance intravenous local anaesthetic blockade

In a preliminary study of 60 patients undergoing minor hand surgery with intravenous regional anaesthesia, the addition of 300 mg of paracetamol to lignocaine decreased tourniquet-related pain and reduced intraoperative pain scores and the need for postoperative analgesia. This result would suggest a peripheral site of action of paracetamol.

Patent ductus arteriosus (PDA) closure

Non-steroidal anti-inflammatory drugs, like ibuprofen and indomethacin, are commonly used as first line medical therapy to close ductus arteriosus with a success rate of 70-80%. Paracetamol has been used instead at doses of 15mg/kg 6 hourly, for 3 days. In some studies this dosing regimen had a similar success rate as NSAID's with a reduced incidence of gastric perforation, renal failure and bleeding commonly associated with NSAID use.

Paracetamol and vaccination

Paracetamol is still the first line drug recommended for pyrexia and constitutional symptoms associated with vaccination. A few studies have however showed reduced immune response and antibody formation after the first vaccine dose. Antibody response is usually similar after a subsequent booster dose and the finding is of unknown clinical significance. It is also the suggested that the timing of antipyretic therapy influence antibody formation. Prophylaxis taken before vaccination had a bigger reduction in antibody titer than a dose taken once symptoms develop. The effect of antipyretics on antibody titers following SARS-CoV-2 have not been studied but certain groups suggest avoiding the prophylactic use of NSAID's and paracetamol.

Notes

Thyroid Physiology

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Introduction

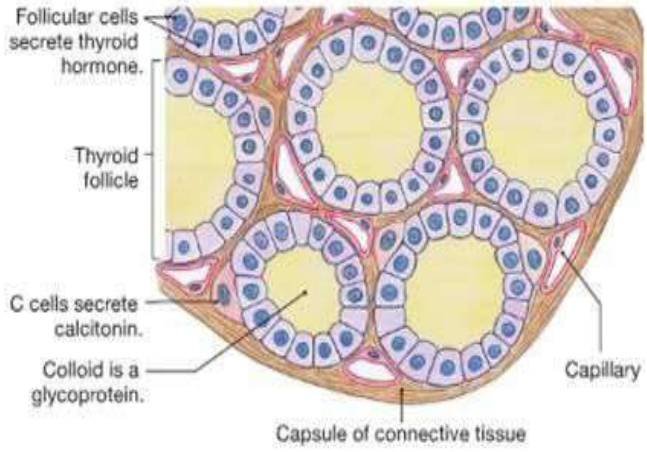
The normal thyroid gland is butterfly shaped and located immediately below the larynx on each side of and anterior to the trachea. Its two lobes are joined by a thin band of tissue, the isthmus, and with an approximate weight of 15-20 g the gland is among the largest of the endocrine organs.

The thyroid gland secretes two major hormones; ***thyroxine*** (T_4) and ***triiodothyronine*** (T_3), which are integral to energy metabolism, growth and homeostasis of most cells in the body. Anatomical disease of the thyroid gland is common, presenting as both benign thyroid enlargement and thyroid malignancy. Furthermore, thyroid hypo- and hyperfunction poses the most common of all endocrine problems, hence the importance of this topic for you as an anaesthetist.

The thyroid also secretes ***calcitonin***, a hormone involved in calcium metabolism, which will not be discussed in this chapter.

A brief account of thyroid microanatomy

The thyroid follicles are the functional units of the thyroid gland where synthesis, storage and secretion of thyroid hormones take place. These units are spherical in structure with an inner core of a secretory substance called colloid surrounded by a single layer of cuboidal epithelial cells - follicular cells. The main constituent of colloid is the large glycoprotein thyroglobulin which contains the thyroid hormones. Scattered between the follicles are the parafollicular cells (C cells) which are the source of the hormone calcitonin.



How are thyroid hormones synthesised?

The function of the thyroid is to generate the quantity of thyroid hormones necessary to meet the demands of the peripheral tissues. For ease of understanding, this process can be split into the following steps:

Synthesis of thyroglobulin; Thyroglobulin (a large glycoprotein containing about 70 tyrosine amino acid residues) is the scaffold upon which thyroid hormone is synthesised. It is formed within the rough endoplasmic reticulum of the follicular cells and secreted into the follicular colloid through exocytosis, where it is stored.

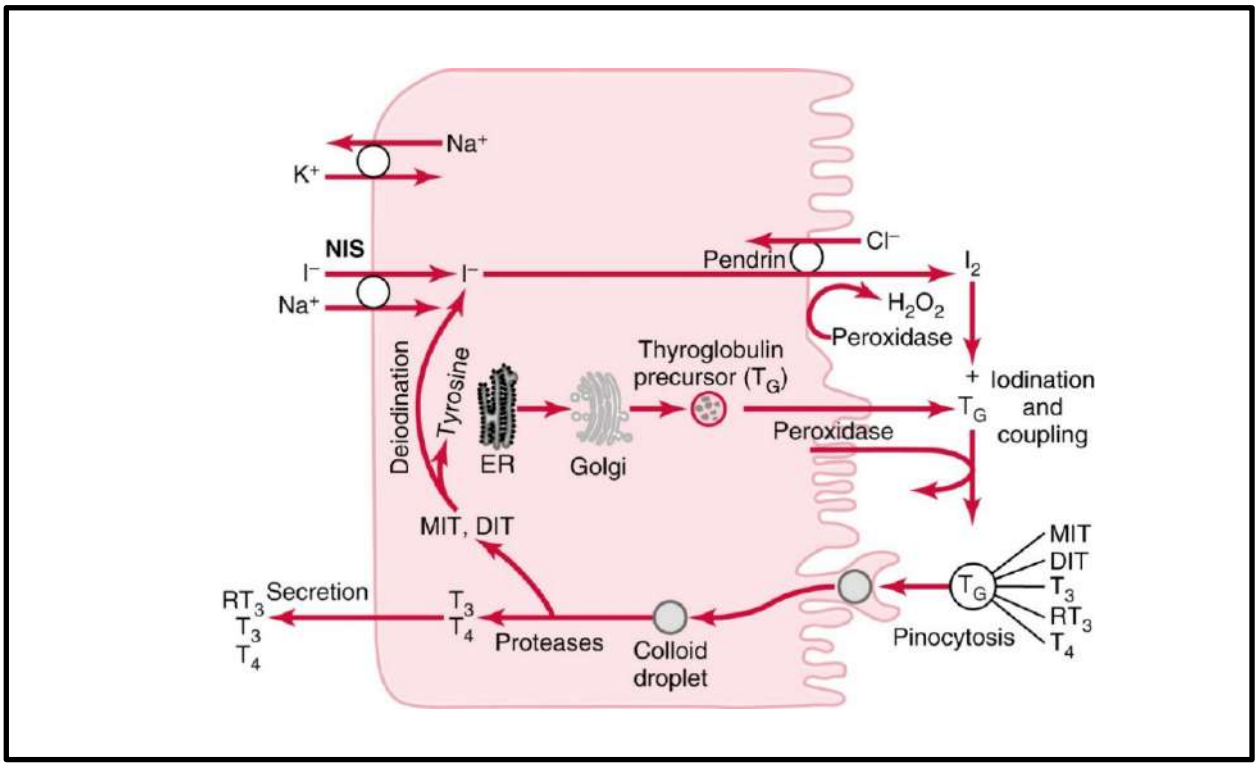
Iodide trapping; Iodine (I_2) is essential to thyroid hormone synthesis. Ingested iodine is reduced to iodide (I^-) and absorbed from the gut. In the thyroid follicular cells, the sodium-iodide symporter (NIS) actively transports iodide from the circulation into the cell against its electrochemical gradient - creating an iodide gradient of 20-40 across the cell membrane. The functionality of the NIS depends on the

presence of a sodium gradient across the basal membrane of the thyroid cell such that downhill transport of two Na^+ ions result in the entry of one iodide atom.

Iodide oxidation; Iodide is transported out of the follicular cell across the apical membrane by a chloride-iodide ion counter-transporter molecule called pendrin. In the interphase between the apical membrane and the colloid, thyroid peroxidase (TPO) promotes the oxidation of iodide to iodine using H_2O_2.

Iodination; Thyroid peroxidase catalyses the iodination of some of the tyrosine residues into iodothyronines on the backbone of the thyroglobulin molecule; a process known as organification of thyroglobulin. Tyrosine may be iodinated at one or two positions, resulting in either monoiodotyrosine (MIT) or diiodotyrosine (DIT). Both are hormonally inactive.

Coupling; Two DIT molecules are coupled to form thyroxine (T_4), the major product of the coupling reaction, and one MIT and one DIT are coupled to form triiodothyronine (T_3). Small amounts of reverse T_3 (RT_3) are also formed but does not appear to be of functional significance in humans.



How are thyroid hormones stored and secreted from the thyroid gland?

The thyroid is unique among the endocrine glands by virtue of its large storage and low turnover rate of its hormones. Thus, the reservoir of thyroxine and triiodothyronine contained in the thyroglobulin molecules provides 2-3 months protection against depletion of circulating hormones in case synthesis ceases.

Hormone release requires the phagocytosis of iodinated thyroglobulin from the colloid into the follicular cells in the form of vesicles, which are then transported to the lysosomes. Within the lysosomes, thyroglobulin undergoes proteolytic degradation releasing thyroxine and triiodothyronine (and reverse triiodothyronine - RT_3) which are then transported out of the cell and into the circulation. About ¾ of the iodinated tyrosine in the thyroglobulin never become thyroid hormones but remain MIT and DIT. During

the digestion of thyroglobulin, iodine is cleaved from MIT and DIT by deiodinases and recycled in the follicular cells.

In a normally functioning thyroid gland, 93% of the secreted thyroid hormones is thyroxine and only 7% is triiodothyronine.

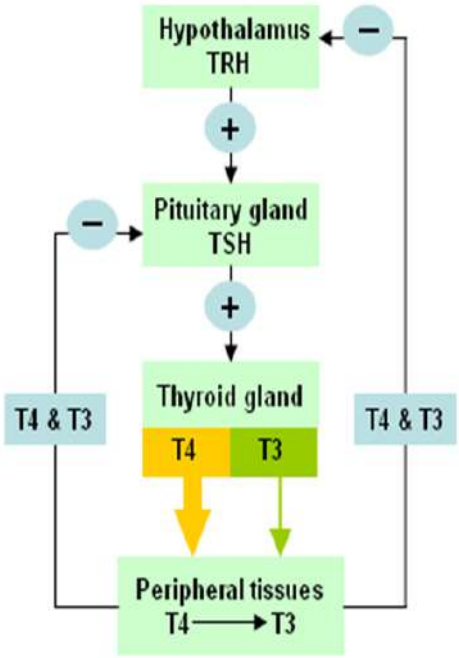
How are the thyroid hormones transported in the circulation?

More than 99% of the hydrophobic thyroid hormones are bound to plasma proteins which ensures uniform tissue distribution; mainly to thyroxine binding globulin (TBG) and a lesser extent to transthyretin and albumin. Thus, the biologically active form of the thyroid hormones - the unbound fraction - constitutes less than 1% of the total plasma concentration.

Due to its strong affinity for the thyroxine-binding globulin, half the thyroxine in the blood is released to the tissue cells about every 6 days, whereas half the triiodothyronine - because of its lower affinity - is released to the cells in about 1 day.

Which factors regulate thyroid hormone secretion?

- Regulation of thyroid function is controlled by the hypothalamic-pituitary-thyroid axis which is characterised as a classic feedback control system.
- Thyroid-stimulating hormone (TSH) from the anterior pituitary gland is the main regulator of thyroid function as it stimulates i. iodine trapping, ii. iodination and coupling, iii. number, size and secretory activity of thyroid cells and iv. proteolysis of thyroglobulin increasing release of thyroid hormones.
- TSH secretion is controlled by i. thyrotropin-releasing hormone (TRH) secreted from the hypothalamus and ii. the blood concentration of unbound thyroxine and tri-iodothyronine.
- An increase in circulating thyroid hormones exerts negative feedback control over the hypothalamus and anterior pituitary, thus maintaining normal plasma level of thyroid hormones by inhibiting the release of TRH and TSH.



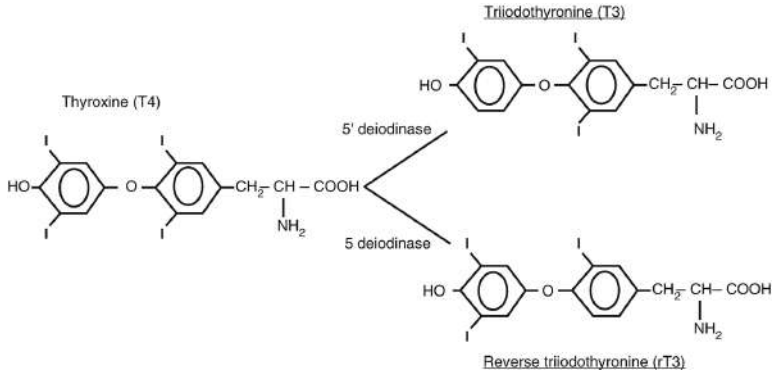
Importantly, to form normal quantities of thyroid hormones, a minimum of 50 mg of ingested iodine are required each year. Furthermore, longstanding exposure to a cold environment stimulates the hypothalamic production of TRH thus increasing TSH secretion, thyroid hormone output and basal metabolic rate (see later). In contrast, prolonged fasting results in reduced plasma leptin levels, which in turn decrease the expression of TRH, TSH and thyroid hormones i.e., contributing to reduced metabolic rate and conservation of energy when food supplies are scarce.

How do the thyroid hormones exert their effects in peripheral tissue?

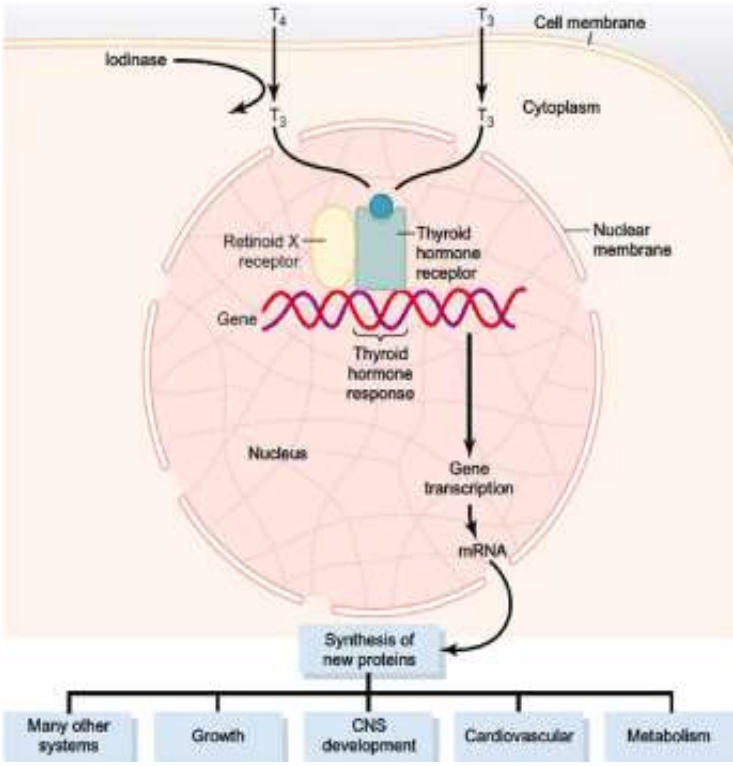
Following proteolytic cleavage from plasma proteins, thyroxine and triiodothyronine cross cell membranes either by diffusion or by carrier-mediated adenosine triphosphate-dependent transport processes.

While both hormones are biologically active, triiodothyronine has stronger receptor affinity and a 3-4 times greater potency per unit weight than that of thyroxine - which explains why triiodothyronine accounts for more than 90% of the binding with intracellular thyroid receptors.

As the thyroid gland only secrets a small quantity of triiodothyronine, the vast majority is sourced from deiodination of thyroxine in peripheral tissue. Iodothyronine deiodinase type 1 and 2 (5' deiodinase) removes an iodine atom from thyroxin's outer ring, producing 3,5,3'- triiodothyronine, while deiodination of the inner ring produces the inactive 3,3',5' - (reverse) triiodothyronine (rT_3). The catalytic site of the deiodinase enzymes contains the rare selenocysteine amino acid, thus selenium is essential for the conversion of thyroxine to triiodothyronine and will, in its absence, manifest as hypothyroidism.



Once inside the cell, thyroid hormones activate nuclear receptors by binding to specific thyroid hormone response elements in the DNA initiating the transcription process. Large numbers of different types of messenger RNA are then formed followed by RNA translation on the cytoplasmic ribosomes to form hundreds of new intracellular proteins. Many of these intracellular proteins are enzymes that promote enhanced intracellular metabolic activity in virtually all cells in the body (see later).



Thyroid hormones also appear to have nongenomic cellular effects in the plasma membrane, cytosol and mitochondria. Their actions include regulation of ion channels and oxidative phosphorylation by activation of intracellular secondary messengers (cAMP/protein kinase signaling cascades).

What are the physiological effects of thyroid hormones in target tissue?

Thyroid hormones are essential in maintaining metabolic activity in almost all human tissues, thus complete lack of thyroid hormone secretion results in a 40-50% fall in basal metabolic rate. Their actions are linked to enhanced mitochondrial size and number as well as regulation of protein, fat and carbohydrate metabolism resulting in enhanced rate and formation of adenosine triphosphate (ATP) to

energize cellular functions. Increasing the rate of metabolism enhances i. cardiac output due to increased vasodilatation and ii. rate and depth of respiration due to increases in oxygen utilisation and carbon dioxide formation.

While thyroid hormones drive a variety of physiological effects (see table below), their involvement in cardiovascular integrity is of particular importance for us as anaesthetists and deserves specific mentioning. In the heart, triiodothyronine binds to specific target genes which code for structural and regulatory proteins (myosin, β-adrenergic receptors, Ca^{2+} - activated ATPase and Ca^{2+}, Na^{+} and K^{+} channels) exerting chronotropic and ionotropic effects. Additionally, thyroid hormones decrease vascular resistance via direct vasodilatation which activates the renin-angiotensin-aldosterone mechanism resulting in increased sodium retention followed by a marked increase in blood volume and further increase in cardiac output.

Target Tissue	Effect	Mechanism
Heart	Chronotropic and Inotropic	Increased number of β-adrenergic receptors Enhanced responses to circulating catecholamines Increased proportion of α-myosin heavy chain (with higher ATPase activity)
Adipose tissue	Catabolic	Stimulated lipolysis
Muscle	Catabolic	Increased protein breakdown
Bone	Developmental	Promote normal growth and skeletal development
Nervous system	Developmental	Promote normal brain development
Gut	Metabolic	Increased rate of carbohydrate absorption
Lipoprotein	Metabolic	Formation of LDL receptors
Other	Calorigenic	Stimulated oxygen consumption by metabolically active tissues (exceptions: testes, uterus, lymph nodes, spleen, anterior pituitary) Increased metabolic rate

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Pathophysiology of the thyroid gland

What are the clinical manifestations of patients with hyperthyroidism?

Regardless of the cause of hyperthyroidism (Graves' disease being the most frequently diagnosed form), the signs and symptoms of thyrotoxicosis are those of a hypermetabolic state;

- A high state of excitability
- Intolerance to heat
- Increased sweating
- Mild-extreme weight loss despite increased food intake
- Diarrhoea
- Muscle weakness
- Nervousness or other psychiatric disorders
- Fatigue but inability to sleep
- Hand tremor
- Exophthalmos or proptosis (specific for Graves' disease)

In our anaesthetic practice, the cardiovascular consequences of increased circulating thyroid hormones are likely to be our main concern;

- Increased resting heart rate which displays an exaggerated increase with exercise is extremely common
- Cardiac output is generally elevated which might lead to aortic flow murmur
- Systolic arterial pressure may be elevated and systemic vascular resistance is reduced leading to wide pulse pressure
- Atrial fibrillation occurs in 5-15% of patients.

How is hyperthyroidism diagnosed?

1. In primary hyperthyroidism, the unbound fraction of thyroxine is increased resulting in decreased plasma levels of TSH as a result of negative feed-back to the hypothalamus-pituitary-thyroid axis.
2. Diagnosis of Graves' disease is confirmed with a high plasma concentration of thyroid-stimulating immunoglobulins - these antibodies bind with the same membrane receptors in the follicular cells as TSH, inducing continual activation of the cAMP-system resulting in unhindered synthesis and secretion of thyroid hormones.

What are the options for medical management of hyperthyroidism?

- First line of treatment is to modify the tissue response to thyroid hormones with thioamides (carbimazole, methimazole or propylthiouracil (PTU)). These drugs interfere with the synthesis of thyroid hormones by inhibiting thyroid peroxidase (iodination of thyroglobulin) and coupling of MIT and DIT. PTU has the added advantage of inhibiting peripheral deiodination of thyroxine to triiodothyronine.

- Iodide in high concentrations inhibits thyroid peroxidase and thus iodination of thyroglobulin and synthesis of thyroid hormones - this is referred to as the acute Wolff-Chaikoff effect. Ipodate (radiographic contrast containing iodine) has the additional benefit of inhibiting the peripheral conversion of thyroxine to triiodothyronine. Treatment effects occur immediately but are short-lived and thus reserved for preparing hyperthyroid patients for surgery, managing patients with actual or impending thyroid storm and treating patients with severe thyrocardiac disease.

- β-Adrenergic antagonists do not affect the underlying abnormality but may relieve signs and symptoms of increased adrenergic activity such as anxiety, sweating, heat intolerance, tremors and tachycardia. Propranolol is the drug of choice as it lacks intrinsic sympathomimetic activity (i.e. will not mimic the symptoms of thyrotoxicosis) and inhibits iodothyronine deiodinase type 1, thus impairing peripheral conversion of thyroxine to triiodothyronine.

- Glucocorticoids (along with the above-mentioned therapies) are administered to patients with life-threatening exacerbation of hyperthyroidism - 'thyroid storm' - to further impair the peripheral conversion of thyroxine to triiodothyronine and to utilise its direct inhibiting effects on TSH and TRH secretion.

What are the clinical manifestations of patients with hypothyroidism?

The effects of hypothyroidism, in general, are opposite to those of hyperthyroidism and is most commonly caused by Hashimoto's autoimmune thyroiditis. This disease is characterised by the production of antibodies against thyroid peroxidase and thyroglobulin, which leads to inflammation and a reduction in functional follicular cells. In regions with dietary iodide deficiency, endemic colloid goiter is the most prevalent form of hypothyroidism, owing to the fact that iodine is an essential substrate for thyroid hormone synthesis.

The clinical characteristics of hypothyroidism are nevertheless the same and depends on how severe the hypothyroid state is;

- ❖ Increased body weight despite lower appetite
- ❖ Slow speech, husky voice
- ❖ Constipation
- ❖ Menorrhagia
- ❖ Cold intolerant
- ❖ Slowing of motor function, fatigue and somnolence
- ❖ Slowing of mental activity/depression
- ❖ Non-pitting oedema (myxoedema) - deposition of mucopolysaccharides in the dermis

Of special interest for anaesthetist, cardiac manifestations include;

- ❖ Bradycardia (most common sign).
- ❖ ECG in patients with overt hypothyroidism shows flattened or inverted T-waves, low amplitude P-waves and QRS complexes.
- ❖ Pericardial effusions
- ❖ Angina (due coronary artery disease from hypercholesterolemia/triglyceridemia)
- ❖ Peripheral vascular resistance is increased and blood volume reduced.
- ❖ Cardiac output is decreased secondary to reductions in stroke volume and heart rate
- ❖ In advanced cases, myocardial contractility becomes reduced secondary to systolic and diastolic dysfunction resulting in enlarged and dilated (hypothyroid) cardiomyopathy

How is hypothyroidism diagnosed?

1. In primary hypothyroidism, low plasma levels of unbound thyroxin results in positive feedback to the hypothalamus-pituitary-thyroid axis, thus leading to enhanced plasma levels of TSH.
2. In Hashimoto's thyroiditis, the presence of antibodies against thyroid peroxidase and/or thyroglobulin confirms the diagnosis.

What are the options for medical management of hypothyroidism?

- First line medical treatment is administration of oral synthetic levothyroxine.

- In the event of emergency surgery in a patient with severe untreated hypothyroidism, the potential for severe intraoperative cardiovascular instability and postoperative myxoedema coma is high. For such patients, intravenous thyroid replacement therapy with triiodothyronine (effective in 6 hours) and glucocorticoid coverage to compensate for decreased adrenal cortical function (which often accompanies hypothyroidism) are two crucial steps in the medical management of severe hypothyroidism.

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Neuromuscular blockers and reversal agents

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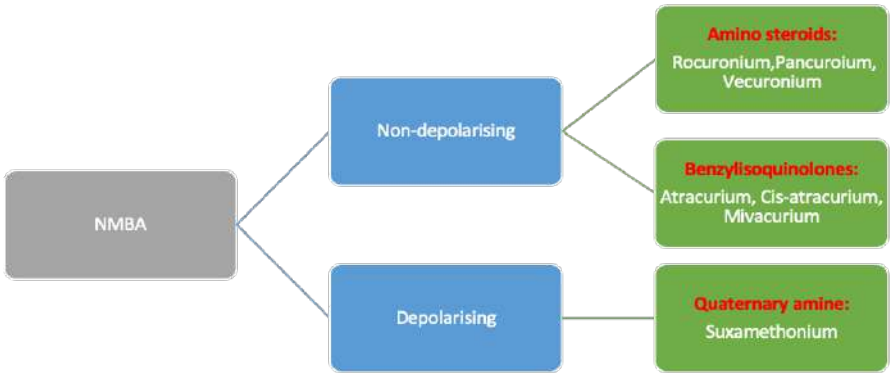
Overview

1. Introduction and clinical use of muscle relaxants
2. Reversal agents - focus on Cyclodextrins
3. Neostigmine vs Sugammadex
4. Residual muscle blockade
5. What is new?

Neuromuscular blockers (NMBA) have been fundamental in creating operating conditions and revolutionized airway management. Before its development, deep muscle relaxation was attempted by deep inhalational anaesthesia, which had a profound cardiopulmonary compromise. The neuromuscular blockade has allowed us to reduce the depth of anaesthesia, create superior airway management for prolonged surgery and optimize patient positioning. It also may decrease the incidence of hoarseness and vocal cord injuries during intubation. It can also facilitate mechanical ventilation in patients with poor lung compliance, as seen in the recent COVID pandemic. Apart from its beneficial effects, muscle relaxation also contributed to new problems arising after its development like awareness, can't intubate can't ventilate scenarios if not used in experienced hands and residual neuromuscular blockade.



Neuromuscular blocking agents are structurally related to acetylcholine (ACh) and contain at least one positively charged quaternary ammonium that binds to the nicotinic receptor.

Depolarizing agents act as agonists like ACh at the nicotinic receptor but cause a more prolonged depolarization of the motor endplate, thus rendering the ion channel insensitive to further action potentials. Non-depolarizing agents compete directly with ACh for nicotinic receptor binding sites and prevent neurotransmitter receptor binding.

Clinical use of NMBA

When choosing an NMBA, the following should be taken into account as these factors affect the response to NMBA:

1. Patient factors (Neuromuscular disease, burns, extremes of age, obesity, hepatic and renal disease
2. Physiological derangement (hypothermia, electrolyte abnormalities, acidosis)
3. Drug interactions: Inhaled AA, Simultaneous use of NMBA's, Antibiotics, Anti-epileptics, Antidepressants and Local Anaesthetic agents

Regarding the use of NMBA at extremes of age, elderly patients have specific changes due to their physiology. Due to the low volume of distribution, decreased hepatic as well as renal blood flow, anatomic changes of the NMJ and altered circulation, the effects might be prolonged. Monitoring of especially the aminosteroids with smaller and less frequent doses is recommended.

Factors that influence the response to NMBA in paediatric patients includes the development of the neuromuscular system, maturation of the transmission of neurotransmitters and development of body systems.

As early as eight weeks gestation, acetylcholine receptors will appear over the human muscle's entire surface. The NMJ will mature from 24 weeks GA but will continue to grow till the first year of life.

Cardiac output and extracellular fluid volume values decline from birth to adulthood. High cardiac output and faster circulation will mean that NMBA acts more rapidly. Increased volume of extracellular fluid and volume of distribution will require increased dosing.

In neonates, accelerometry can't be used because the small motions of the infant's thumb are not sensitive enough for these monitors.

Reversal agents

The ideal agent can reverse any neuromuscular blocker at any depth of block with a rapid onset at maximal effect. It is free of adverse muscarinic effects, histamine release, not dependent on the elimination of organ systems, inexpensive, available in a solution, not producing depolarizing blocks in excess and has no ceiling effect. We still need a drug that fulfils all these criteria.

Cyclodextrins

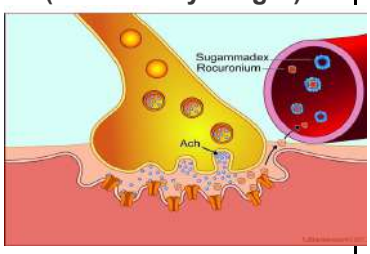
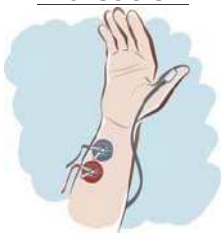
Cyclodextrins is close to the ideal agent because it offers rapid and complete reversal of neuromuscular blockade at any depth. It has a reasonably fast onset dose-dependent but is expensive, cannot be used in patients with renal impairment. It also only reverses aminosteroid NMBAs.

Sugammadex

Sugammadex is an encapsulating cyclodextrin. t encapsulates aminosteroid neuromuscular blockers like Rocuronium in a 1:1 ratio. After encapsulation, it rapidly decreases the plasma concentration of the free drug, promoting its dissociation from the NMJ and restoring motor tone.

This cyclodextrin has eight oligosaccharides attached by a 1–4 linkages into a circular arrangement to create a hollow toroid. Sugammadex has a hydrophilic negatively charged outer surface and lipophilic inner surface. The negatively charged outer surface strongly attracts the positively charged quaternary ammoniums of the Rocuronium. These get drawn to the lipophilic central core. Inside they are tightly held due to van der Waals forces and the charge, until the inactive, water-soluble complex is eliminated by the kidneys. Currently there is no evidence that patients with end-stage renal disease will have different kinetics, but it is not recommended on the package insert. The affinity of Sugammadex for Rocuronium is comparable with the affinity of acetylcholine for the postsynaptic nicotinic receptor.

Sugammadex dose of reversal of NMB

Sugammadex dose (actual body weight) 	**Indication** 	**Avg time to TOF 0.9** 
16mg/kg	Immediate reversal after Rocuronium 1.2mg/kg No twitches	**1.5 min**
4 mg/kg	Reversal of deep NMB TOF 0 PTC ½	**3 min**
2 mg/kg	Reversal moderate NMB TOF 2	**2 min**

After the administration of a standard dose of Rocuronium (0.6 mg/kg), spontaneous recovery will occur after approximately 2 hours to achieve a TOFR= 0.9. The dose is dependent on the degree of block. Sugammadex 2mg/kg will accomplish this in 100 sec when reversing a moderate block of TOFR 0.2. A more profound block (PTC 2-4) will require a recommended dose of 4-8mg/kg. In a "can't intubate, can't ventilate' scenario, 16mg/kg will reverse Rocuronium immediately.

Drug interactions of Sugammadex may occur because it encapsulates opioids, hydrocortisone, verapamil and atropine, as well as the displacement of Toremifene and Flucloxacillin. This encapsulation is, however, 700 times less than for Rocuronium and of questionable clinical significance.

Interesting facts about Sugammadex

In laparoscopic procedures, the use of a profound NMB improves surgical operating conditions and allows lower pressure pneumoperitoneum, less postoperative pain and discomfort of the shoulder tip. Profound blocks can be reversed with Sugammadex. This might be especially helpful in bariatric surgery.

Sugammadex doses up to 16mg/kg were associated with clotting abnormalities, especially in patients being treated with anticoagulation. An increase in the APPT and INR was observed. Careful monitoring of coagulation is advised.

The FDA has approved Sugammadex for reversal of NMBA in children older than two years.

Redosing of NMBA after Sugammadex

When NMB is required before the waiting time has elapsed, it is recommended to use a non-steroid NMBA. Of note is that depolarizing NMBA's onset of action might be slower because the receptor still occupies the nicotinic receptors on the post-junctional membrane.

When steroidal NMBA is used, expect a delayed onset and shorter duration of action. The recommended waiting time for the re-administration of Rocuronium after 16mg/kg of Sugammadex is 24hrs.

Recommended waiting time for re-administration of Rocuronium after Sugammadex.

	Sugammadex ≤4mg/kg		Sugammadex 16mg/kg
NMBA	Min waiting time Normal renal function 	Min waiting time Mild-mod impaired renal function 	Min waiting time 
Rocuronium 1,2mg/kg	5 min	?	24 hr
Rocuronium 0,6mg/kg	4 hr	24 hr	24 hr

Residual muscle blockade

Residual muscle blockade has a wide incidence range of 4-50%, depending on the diagnostic criteria and type of NMBA used. This clinically relevant problem is associated with muscle weakness, desaturation, pulmonary atelectasis and acute respiratory failure. This may lead to brain death or permanent brain damage. The aim at emergence is the absence of residual paralysis so that sufficiently recovered patient can breathe unaided, clear secretions, cough, prevent aspiration and maintain.

Clinical and neuromuscular tests are used to identify residual muscle paralysis. Of note is that none of the clinical tests was found as reliable and sensitive enough. Neuromuscular tests are the mainstay, with specific emphasis on the quantitative measure of TOFR. This method is trustworthy and mainstay. Note that a TOFR of >1 is necessary to exclude residual paralysis.

Relevance of Complications associated with residual paralysis.

Apart from the well-known respiratory complications associated with residual paralysis, death, or permanent brain damage has been documented in studies. The most common cause of death attributable to anaesthesia is respiratory depression. Some studies mentioned that death due to anaesthesia was increased tenfold when the reversal was omitted.

Regarding pulmonary complications, a 3 -fold increase in atelectasis was noted when patients received long-acting NMBA.

Severe hypoxemia, respiratory failure and upper airway obstruction were frequently found adverse events in the PACU. Neuromuscular recovery is an essential factor in respiratory adverse events.

There was a strong association between residual paralysis defined as a TOFR <0.9 and postoperative hypoxaemia.

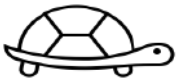
Residual paralysis is an avoidable complication, and the risk decreased by careful monitoring and judicious administration of reversal agents. In this way, many of the deleterious clinical consequences are avoided.

Clinically Relevant Complications associated with Residual Paralysis

Complication	Key message
Death/Permanent brain damage	Respiratory depression is the most frequent cause of death due to anaesthesia. (Tiret et al.)
	Relation possible between postoperative respiratory depression and NMB (Lunn, Cooper et al.)
	10-fold increase when reversal omitted (Arbous et al.)
Pulmonary complications	3-fold increased atelectasis in long-acting NMBA with residual paralysis (Berg et al.)
Reintubation due to Upper airway obstruction, severe hypoxemia or respiratory failure	Incomplete recovery an essential contributing factor in PACU adverse events (Murphy et al.)

Adjusted from Residual Paralysis after Emergence from Anesthesia

Sugammadex vs Neostigmine

	Neostigmine 	**Sugammadex** 
Cost	R6.30 per amp + (Glycopyrrolate: R19.60)	R760 per amp 200mg
Return to TOF >0.9	17.9 min	2.7 min
Major pulmonary complications	Controversial	30% ↓ pulmonary complications (STRONGER trial) No difference (POPULAR trial)
Drug interactions	Antibiotics	COC, SERMS
Ceiling effect	Yes	Increase dose depending on depth of NMB
Time to max effect	8 min	Dose-dependent
Renal insufficiency	Prolonged muscarinic effect	Use not advised in severe renal dysfunction
Anticholinergic S/E	Yes	Vagal effect(? mechanism)
Anaphylaxis	Very rare NAP 6: no reports	NAP 6: 0.0016%
Elimination t 1/2	50-90 min	180 min
Agents reversed	All Non-Depolarizers	Only aminosteroids: Roc>Vec>Pank

Sugammadex vs Neostigmine and Pulmonary complications

The use of any neuromuscular blocking agent is associated with post-operative pulmonary complications (POPC). There is conflicting evidence about the use of Neostigmine, as some studies suggest this increases the risk of POPC. However, incomplete recovery is a more significant contributor to POPC than the use of Neostigmine or Sugammadex, respectively.

Residual neuromuscular blockade after inadequate reversal is an independent risk factor for anaesthesia related morbidity and mortality in the 24hrs post-operatively.

Newer evidence suggests a TOFR of 0.95 should be targeted before extubation as this will decrease the incidence of POPC with or without a reversal agent being used.

POPC leading to hypoxemia, length of hospital stay is more common in elderly patients. Elderly patients had almost twice as much residual block compared to younger patients.

Residual paralysis is an avoidable complication, and the risk decreased by careful monitoring and judicious administration of reversal agents. In this way, many of the deleterious clinical consequences are avoided.

What is new?

The search for the perfect neuromuscular blocker and reversal agents is still ongoing.

Chlorofumarates

A new benzylisoquinolinium that breaks down spontaneously in plasma and does not depend on organ function, with short onset time without cardiovascular effects. Gantacurium has an onset of action similar to Rocuronium and a very short duration of action like suxamethonium. Major histamine release stopped its development. Two other Chlorofumarates are currently under trials. Reversal with Neostigmine is possible, but more rapid reversal with L-cysteine, a preparation available for use in parenteral nutrition currently.

Calabadion 1 and 2

An effective reversal agent for aminosteroids and benzylisoquinolines brought on the investigation to these products. They have a similar mechanism of action to Sugammadex. Studies of these new compounds in humans are still not undertaken.

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Notes

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Developmental Pharmacology
Applications for Anaesthetists

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Introduction

Neonates, infants, and children have generally been neglected as populations in drug research. Estimates suggest that up to 90% of drugs administered to children have not been formally studied in the paediatric population. The highest percentage of off-label drug use occurs in infants under a year of age. Neonates, infants, and children demonstrate pharmacological changes which may affect the optimal drug administration and dosage. Understanding the difference in pharmacology in this population is needed for the safe and effective administration of anaesthesia and analgesia.
We have long recognised that linear dosing results in under-dosing small children. Dosing regimens for many drugs have been derived empirically from adult doses using scaling methods based on characteristics such as body surface area or body weight and subsequently fine-tuned with clinical experience. Extrapolating pharmacokinetic data from older children and adults is generally unsuccessful due to the complex physiological differences in neonates and infants.
Developmental pharmacology is an expansive field that incorporates the changes in both the pharmacokinetics as well as the pharmacodynamics of drugs during growth and development. Many of the changes in pharmacology in children and infants can be described by how ontogeny affects both pharmacokinetics as well as pharmacodynamics. Ontogeny is the growth (size change) and development (structure change) of an individual organism. Growth and maturation of organ function and metabolic processes characterise early development.

How does growth affect pharmacology?

Growth is a dynamic process that results in changes in stature, body proportion, and composition. It incorporates cell hyperplasia, cell hypertrophy, and apoptosis. A wide variety of genetic, secular, socioeconomic, and environmental factors influence growth.
Postnatal growth follows three typical curves. Rapid growth occurs during the first three years, followed by a slowly decelerating childhood component and a rapid growth phase or spurt in adolescence. Growth rates decline from 20 cm/year in the first few months to 10–12 cm/year by the first year of age, by which time length has increased 50%, and weight has tripled. The growth rate then declines slightly throughout childhood until the pubertal growth spurt (Fig 1.).
Growth is, however, an energy-intensive process that requires extensive physiological adjustments to occur. Increased supply of nutrients and removal of waste products necessitates an increase in cardiac index. At term, the neonatal cardiac output is approximately 200 ml/kg/minute, almost three times that of adults, and by two-years still 50% more than an adult. Changes in cardiac index tend to mirror the growth curves.
Increases in cardiac index affect drug distribution and elimination clearance, particularly in drugs with a high hepatic extraction ratio. Variations in cardiac output affect the pharmacokinetics of a drug affecting both peak and steady-state plasma drug concentrations. An increased cardiac index may require an increased dose per kilogram to achieve the desired effect. Increased doses may prolong the context-sensitive half-times.
Regional cardiac output distribution further complicates the issue.
As growth rates decline, children over the age of 3 behave more like little adults. Physiological and pharmacokinetic features become more predictable from adults based solely on weight.

Maturation of organ function and metabolic processes

Clearance and elimination are not linearly related to weight, metabolic rate, and cardiac output. Neonates and infants have immature renal and metabolic drug elimination pathways. Maturation of enzyme systems begins before birth, and rapid maturity in drug metabolism occurs in the neonatal period. This affects the safety and efficacy of drugs related to the various pharmacokinetic phases (absorption, distribution, metabolism, and excretion).

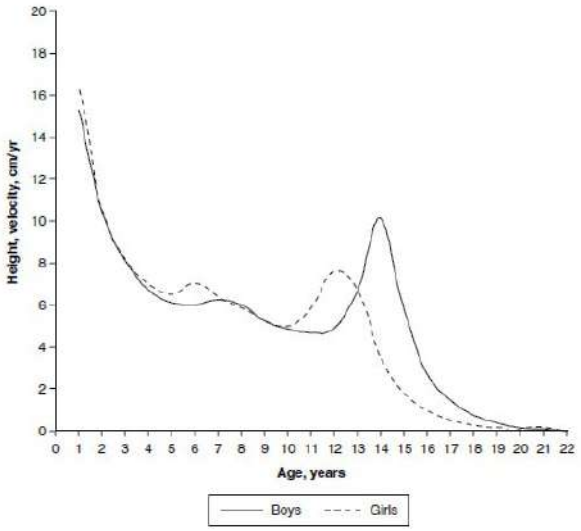

Figure 1 Idealised velocity growth curves

Developmental changes in pharmacokinetics

Developmental changes occur across the pharmacokinetic processes of absorption, distribution, metabolism, and excretion. Paediatric pharmacokinetic and pharmacodynamic processes reach adult equivalents at different ages. These developmental changes are also affected by various factors, including concurrent pathology, malnutrition, and prematurity.

Drug absorption

Whereas most anaesthetic agent delivery occurs via inhalational or intravenous routes, most other drug administration to neonates occurs via the oral route. Drug characteristics and developmental changes in surfaces of the gastrointestinal tract, lungs and skin affect absorption. Gastric pH influences drug stability, dissolution, and ionization. These all have an impact on drug absorption. At birth, gastric pH is neutral due to amniotic fluid in the stomach and then remains less acidic until about 3-years of age when the pH approaches adult values. Age has minimal influence on intestinal transit time, and gut mobility is more dependent on food type. Developmental immaturity in intestinal transporters and enzymes may affect the absorption of drugs. Transporters serve as mechanisms to move compounds out of the intestinal epithelium and return them to the intestinal lumen and modulate drug absorption. Intestinal enzymes, on the other hand, are responsible for some metabolism of orally ingested drugs. Several enzyme systems are present within the intestinal cell, of which the cytochrome P450(CYP) appears to be the most important. Premature infants have a low first-pass effect by intestinal and hepatic metabolism by CYP3A. The result is a high bioavailability of CYP3A substrates such as midazolam. The developmental patterns of most of the intestinal enzymes and the clinical implications of their ontogeny remain unknown.
Developmental changes affect the skin throughout infancy and childhood, influencing the rate and extent of absorption, metabolism, and bioavailability of topical medications. Preterm infants exhibit increased cutaneous permeability and immature vasomotor control. Increases in skin hydration result in enhanced permeability of the stratum corneum. Increased permeability is most prominent in the axillae, groin, and flexor surfaces of the limbs, intensifying topical absorption of drugs. An increased total body surface area to body mass ratio in the neonate further enhances topical absorption of drugs. The skin may comprise up to 13% of a premature infant's body weight compared to 3% of an adult's body weight. Topical use of the local anaesthetics cream EMLA® for pain relief may lead to methaemoglobinaemia in neonates. Increased systemic absorption and susceptibility of foetal haemoglobin to prilocaine seemingly the culprits.

Distribution

After reaching the systemic circulation by whichever route, the administered drug will distribute into different tissues and organs. Distribution patterns will depend on the drug's physical attributes, age-

related developmental changes in body composition, protein binding, pH, blood flow, and the permeability of physiological barriers (e.g., The blood-brain-barrier).
Changes in body composition influence the distribution of drugs. Body composition is a crucial determinant of the distribution of drugs. Total body water content in neonates approaches 80%, which rapidly declines in the first months of life to the adult fraction of 60%. At birth, neonates have a higher fraction of extracellular water, steadily declining throughout childhood. An increase in total body water increases the volume of distribution for hydrophilic drugs. The result is the need for a larger loading dose (per kg) to achieve therapeutic levels (e.g., aminoglycosides).
The fat and muscle content in the neonate is relatively low. The fat component increases significantly in early infancy and then steadily declines to near-adult values by 3-years of age. These changes explain the reduced volume of distribution of lipophilic compounds in the new-born compared to older infants. Drugs that rely on redistribution to fat and muscle, such as fentanyl, thiopentone or propofol, will have prolonged and higher plasma concentrations in neonates. Exaggerated body composition changes occur in the premature neonate, with the total body water decreasing from 85% in preterm neonates to 75% in term neonates.

Changes in the composition and the amount of circulating plasma proteins can alter the distribution of drugs. Neonates and children under 2-years of age have lower total concentrations of plasma proteins (albumin, α-1 acid glycoprotein, and plasma globulins) and a reduced ability of these proteins to bind to drugs. Lower plasma proteins influence the amount of free drug available for distribution in the body and pharmacological effect. As plasma proteins do not readily leave the intravascular space, reductions in circulating proteins will increase the volume of distribution of protein-bound drugs. Decreased protein binding in premature and term neonates compared to older children results in greater free-drug concentration and increased drug effect (and potential toxicity) in highly protein-bound drugs. Because protein concentrations reach adult values in infancy, this effect is most pronounced in neonates and younger infants. Drugs (propofol, phenytoin, diazepam, ibuprofen) undergo competitive binding by bilirubin for albumin. Competition may result in either further increased free-drug concentration or increased free bilirubin. The latter could potentially increase the risk of kernicterus in neonates.

Developmental differences in regional and systemic blood flow influence drug distribution. Changes in cardiac index affect the distribution of a drug by changing intercompartmental clearances of the drug. For drugs with a high hepatic extraction ratio, changes in cardiac index affect liver blood flow and therefore influence their elimination clearance. Changes in the pharmacokinetics of a drug resulting from changes in cardiac output may affect both early and steady-state arterial drug concentrations as well as the context-sensitive half-time. An increase in the cardiac index as seen in neonates and infants results in pharmacokinetic changes. Systemic concentrations of an intravenously administered drug are inversely related to the cardiac index. A high cardiac index necessitates a similarly high venous return. This increased venous return rapidly dilutes the drug resulting in a lower-than-expected plasma arterial concentration. Doses required to maintain a target plasma concentration increase with increasing cardiac output as clearance is increased. Clearance may initially increase due to redistribution of a drug in tissues leading to an increase of the context-sensitive half-time for the drug.

Metabolism and elimination

Drug metabolism is an essential step in drug activity and clearance. The main routes by which drugs and their metabolites leave the body are the hepatobiliary system, the kidneys, and the lungs. Drug metabolism may occur in many tissues (gastrointestinal epithelial, renal, skin, and lung tissues), the liver being the predominant site. Metabolism usually converts drugs to water-soluble compounds. These compounds are subsequently easily excreted by the renal or biliary route. Patients who have delayed clearance are at risk for drug accumulation and toxicity. They may require changes in dose or dosing interval. In general, the rate of drug elimination by biotransformation in neonates and infants is slower than in adults. The predominant pathways involved in hepatic drug metabolism are commonly divided into either phase I or phase II reactions.

Phase I reactions increase the polarity of the compound by introducing or exposing functional groups on the molecule. Phase I reactions are broadly grouped into three categories, oxidation, reduction, and hydrolysis. Quantitatively the most significant phase I reactions are represented by the cytochrome P-450 system. Development significantly changes the expression of the cytochrome P-450, and the phenotypic activity is primarily dependant on age. The CYP-dependent metabolic capacity at birth is 30–60% of adults. Enzyme activity increases significantly subsequently, and CYP

activity matures by 2-years of age. Decreased activity of cytochrome P-450 system results in toxicity syndromes seen in premature infants, such as grey baby syndrome with chloramphenicol and gasping syndrome with benzyl alcohol.
In humans, seven isoenzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6 CYP3A4) are responsible for the metabolism of more than 95% of drugs. Of these, the CYP3A accounts for the metabolism of at least 50% of therapeutic drugs given.

At birth, CYP1A2, responsible for caffeine-3-demethylation, has negligible activity. The half-life of caffeine is 72‑96 hours in new-borns compared with approximately 5 hours in older children. CYP1A2 is induced rapidly after birth with postnatal age correlating with changes in half ‑ life and clearance.

CYP3A4 is functionally immature after birth. Enzyme activity starts to increase after 2-weeks post ‑ natal age to reach 30‑40% of adult values by 4-weeks of age. CYP3A4 reaches adult levels by around 3-years of age. Neonates depend on the immature CYP3A4 for clearance of levobupivacaine and midazolam and CYP1A2 for ropivacaine clearance. The reduced metabolic clearance of local anaesthetic results in potential increased toxicity in this age-group and necessitates reduced epidural infusion rates. Midazolam, in neonates, is also cleared by CYP3A4, resulting in an increased duration of sedation.

Enzyme	Neonate	One month	3 months	6 months	1 Year	10 Years
CYP3A4	0.24	0.5	0.7	1.1	1.3	1
CYP1A2	0.1	0.2	0.25	0.29	0.35	1
CYP2E1	0.32	0.4	0.46	0.46	1	1

Table 1. Enzyme activity (expressed as fraction of adult values) as a function of age.

Enzyme	Drug examples	Comments
CYP 1A2	Caffeine Paracetamol Ropivacaine	Absent-to-low expression in the neonate; activity reaches 50% of adult values by 1 y of age; formula-fed infants have faster maturation.
CYP 2D6	Lignocaine Codeine tramadol	Usually present at 1-week postmenstrual age but only 20% of adult activity at 1 month. Variable because of genetic polymorphism: up to 47% of 3-12 year cannot convert codeine to morphine
CYP 2C9	Ibuprofen	
CYP 3A4	Midazolam Bupivacaine	Low expression at birth; increases to 30% adult levels by 1 month; almost fivefold increase by 3 months; full adult activity reached by 6 months; formula fed infants may have faster maturation.
CYP 2E1	Paracetamol	Approximately 10% of adult activity in the neonate; steadily increases to 30% by 3–12 months; reaches adult levels between 1–10 y of age.

Table 2. Developmental expression of selected drug-metabolizing enzymes in the neonate

Phase II reactions are conjugation reactions; they occur by coupling the drug or its metabolites to another molecule. The molecule binds to the reactive site of the Phase I metabolite. Phase II products are usually hydrophilic and readily eliminated from the body. Conjugation reactions are reactions that include glucuronidation, sulphation, methylation, or acetylation. Maturation of phase II conjugation enzyme activity occurs at a much less predictable pace. The largest groups of enzymes involved in phase II reactions are uridine diphosphate glucuronosyltransferase (UGT) isoenzymes. Some phase II pathways like sulphate conjugation are mature at birth. Others like acetylation, glycation, glucuronidation are immature. Before glucuronidation matures, sulphate conjugation acts as an alternative route. Sulphate conjugation is an active metabolic pathway in neonates for morphine and paracetamol. Glucuronidation activity reaches adult values between 2 and 6 months for morphine. Clearance increases in early life as hepatic glucuronidation enzyme pathways mature. Glucuronidation is a major metabolic pathway of propofol metabolism. Multiple cytochrome P450 isoenzymes, including CYP2B6, CYP2C9, or CYP2A6, also contribute to its metabolism resulting in a faster maturation profile than glucuronide conjugation alone.

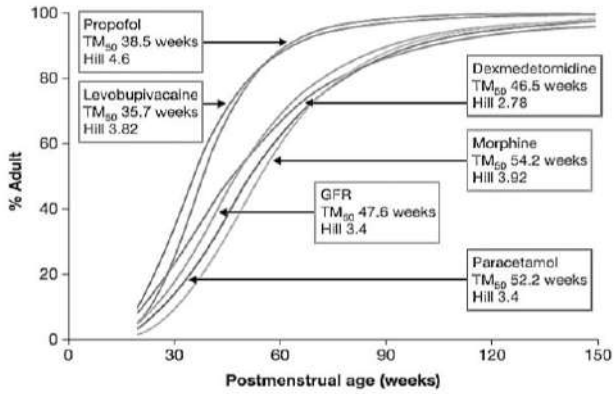

Figure 2. Clearance of paracetamol, morphine, dexmedetomidine, propofol and levobupivacaine as a % of adult values.

Drug elimination

Drug elimination occurs via multiple routes and includes biliary excretion, exhalation, and renal clearance. Renal excretion is a dominant path of drug elimination. Non-volatile, water-soluble, and low molecular weight drugs generally follow this route. Renal function is immature at birth. Reduced renal blood flow, reduced concentrating capacity of the renal tubules, lower glomerular filtration rate (GFR), and reduced tubular secretory ability contribute to this. Of these, the reduced GFR is the most important determinant of renal drug clearance. The most important factors that influence GFR at birth are postmenstrual age, prenatal nephrotoxic drug exposure, and the presence of a patent ductus arteriosus. Renally excreted drugs in neonates are eliminated more slowly, with an increased risk of adverse events.
The GFR increases rapidly during the first weeks of life. The increase is due to reduced renal vascular resistance and a subsequent increase in renal blood flow. GFR rises steadily until adult values at 8 to 12 months of age. The most crucial factor that leads to an increase in GFR is the increase in glomerular surface area. Parallel increases in tubular solute and water reabsorption balance the increased surface area to prevent volume depletion - designated glomerulo-tubular balance. Premature neonates exhibit some glomerulo-tubular imbalance evidenced by glucosuria, with normal serum glucose levels. Tubular secretion and absorptive capacity approach adult values by 7–12 months of age.

Population based pharmacokinetics

As mentioned earlier, the development of dosing schemes in neonates, infants and children are more demanding than in adults. A scarcity of pharmacokinetic data and the fact that clinical trials are challenging to conduct in neonates contribute to these difficulties. Most dosing schemes are either age-related or scaled by a variety of methods. Scaling methods include:

- Normalising for bodyweight - per kilogram scaling from adult doses
- Normalising for fat-free mass (FFM)
- Normalising to body surface area – per m^2 scaling from adult doses
- Allometric methods

All these methods have a sound physiological basis but do not account for developmental and maturational changes occurring in childhood. None of these methods correlates well with pharmacokinetic parameters such as drug distribution. Weight-based dosing may result in the under-dosing of infants and children. Body surface area dosing often overestimates the dose for infants. Dosing requirements are often substantially different from adults when drugs undergo studies in children. Data extrapolated from adult studies cannot explain the correlation between drug effect and drug administration in children.

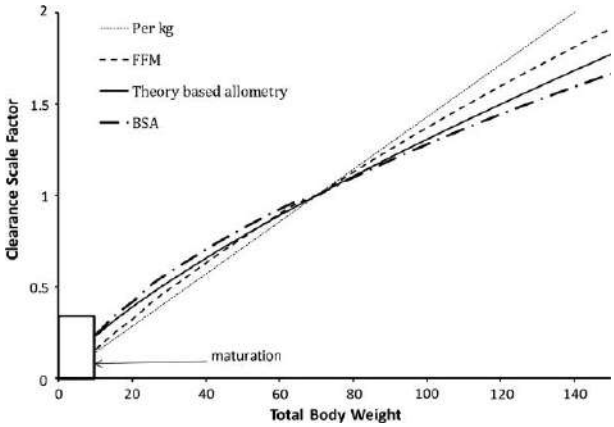

Figure 3. Body size metrics used to describe clearance changes with weight for individuals of average height for weight. The clearance scale factor shows how clearance would differ with weight. A non-linear relationship exists between weight and clearance using theory-based allometry. The per kg method increasingly overestimates clearance in adults and underestimates clearance in children. The body surface area method overestimates clearance in children compared with theory-based allometry. Scaling with fat-free mass lies between the per kg method and theory-based allometry.

A physiologically based pharmacokinetic model predicts the pharmacokinetic parameters in a specific population group. PBPK models simulate the disposition of a drug in the body by following the principles of mass transport, fluid dynamics, and biochemistry. PBPK models envisage the body as a network of compartments representing individual organs or tissues interconnected by the arterial and venous blood flow. Biochemical and physicochemical parameters such as protein binding, blood-to-plasma ratio, and tissue-to-blood partition coefficients are determined. New data from patients receiving the drug strengthen PBPK models by incorporating disease-specific changes in the pharmacokinetics. Specific sampling is not critical for population pharmacokinetic studies as samples taken as part of routine clinical care can be used, limiting the number of specimens required from each subject. The introduction of these PBPK models reduces the burden on a patient involved in a pharmacokinetic study. Whilst still an evolving field and not perfect, PBPK modelling will become an even more important tool in successfully predicting the effect of drugs in neonates, infants, and children.

Developmental Pharmacodynamics

Developmental pharmacodynamics is the study of how age-related development affects drug response in terms of both anatomical structure and function. Developmental pharmacodynamics describes age-related changes in the potency, efficacy, or therapeutic range of a drug and are generally related to ligand-receptor interactions. Age-related changes affect receptors both quantitively and qualitatively.
Qualitative changes include receptor subtype, density, distribution, and ligand affinity. Research and data regarding the effects of human ontogeny on pharmacodynamics are unfortunately limited.

Developmental changes in γ-aminobutyric acid (GABA) receptors occur in both animals and humans. In the adult brain GABA, via activation of the $GABA_A$ receptor, mediates the majority of fast inhibitory neurotransmission in the central nervous system. GABA is, however, excitatory in the developing foetal brain. GABA excitation occurs by depolarizing developing neurons that have high chloride concentrations. During maturation, the chloride concentration decreases, resulting in an opposite effect of GABA. $GABA_A$ receptors display significant structural heterogeneity assembled from a repository of at least 18 subunits. Maturation of receptor expression occurs over the first 5 to 6 years of life before reaching a plateau. Age-related changes in the $GABA_A$ subtype expression may explain dosing anomalies in infants. Infants may require larger doses of anti-epileptic drugs. Paradoxical seizures in infants may occasionally occur after exposure to benzodiazepines. Other developmental GABA mediated effects may also explain the emergence agitation seen in children and increased inhalational anaesthetic requirements in early infancy.
Neuromuscular transmission is immature at birth. In developing motor neurons, reduced acetylcholine concentrations enhance sensitivity to non-depolarizing neuromuscular blocking drugs (NMBDs). The plasma concentration of NMBDs required to produce neuromuscular paralysis is lower. The volume of distribution at a steady state for muscle relaxants is greater in neonates than in the other age groups. Fortunately, these two pharmacokinetic and pharmacodynamic phenomena cancel each other out. Increased pharmacodynamic sensitivity balances a larger volume of distribution.

Increased postnatal expression of the mu-opioid receptors may result in increased sensitivity of neonates to morphine. Receptor expression, however, may not necessarily correlate with receptor activation. Multiple other structural difference in the neonatal central nervous system result in complex changes to developmental pharmacodynamics.

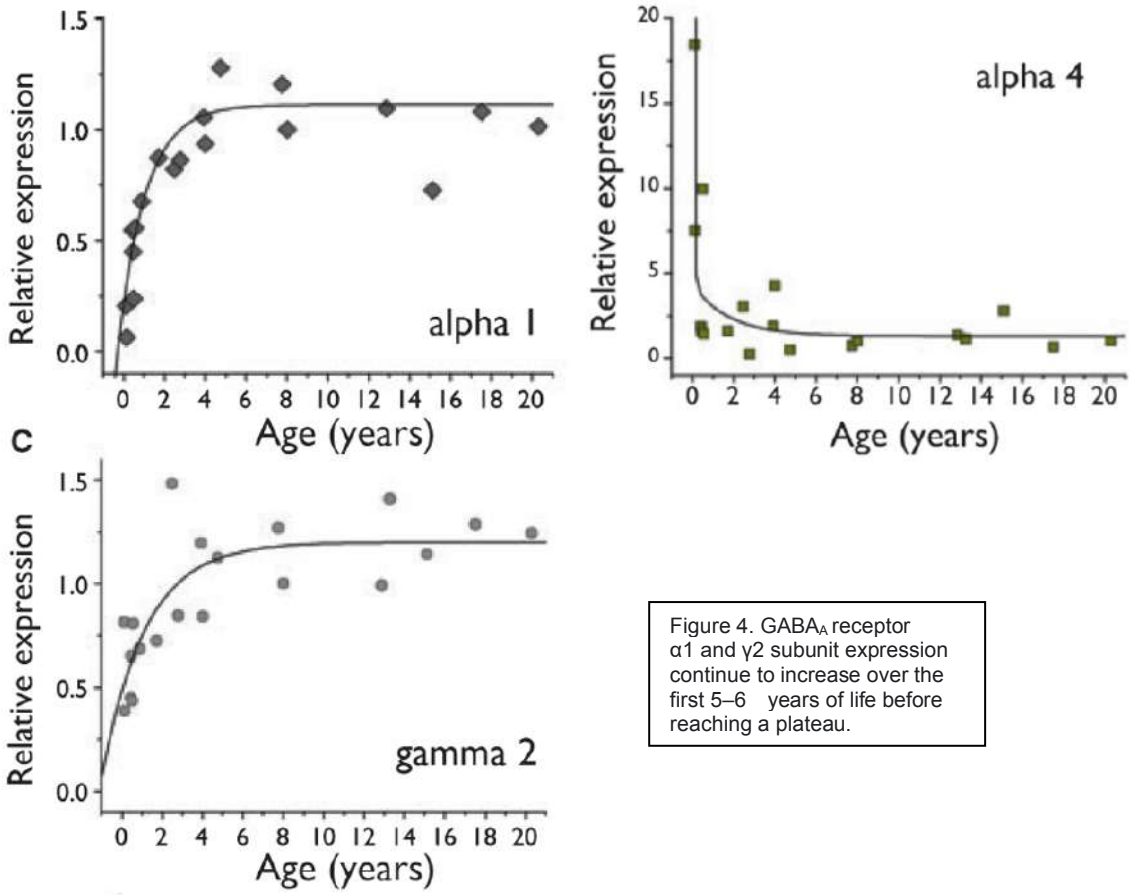

Figure 4. $GABA_A$ receptor α1 and γ2 subunit expression continue to increase over the first 5–6 years of life before reaching a plateau.

Pharmacogenetics

Pharmacogenetics is the science of how genetic variability influences drug-treatment outcomes. The terms pharmacogenetics and pharmacogenomics are used interchangeably. Pharmacogenetics refers to the effects of a single genetic marker. Pharmacogenomics is broader in context, referring to the collective influence of variability across the genome. Inter-individual pharmacokinetic variability that is contributed to by polymorphisms of the genes encoding for metabolic enzymes is very large. Table 3 highlights some examples that affect commonly used anaesthetic agents.

Drug	Gene	Allele	Effect Associated with Allele
Halothane, other inhalation anaesthetics	CYP2E1	Unknown	Hepatitis
Halothane, isoflurane, succinylcholine	RYRI	223 different mutant alleles	Malignant hyperthermia syndrome
Succinylcholine, mivacurium	Plasma butyrylcholinesterase	"Atypical" allele "Silent" allele	Prolonged muscle relaxation
Diazepam	CYP2C19	G681A	Increased half-life, prolonged sedation, greater likelihood of unconsciousness
Midazolam	CYP3A4	A290G (*1B)	Reduced clearance of systemic (but not oral) midazolam
Midazolam	CYP3A5	A22893G (*3)	Reduced clearance of systemic (but not oral) midazolam
Morphine, morphine-6 glucuronide	mu-Opioid receptor	A118G	Reduced nausea, vomiting, sedation, drowsiness
'Morphine	Uridine diphosphate glycosyl transferase	C-161T and C802T	More rapid glucuronidation

Codeine	CYP2D6	G 1846A (*4) Deletion of gene (*5) 1707T>del (*6)	Slower conversion of codeine to morphine; reduction in analgesic effect (but not adverse effects)
Tramadol	CYP2D6	G 1846A (*4) Deletion of gene (*5) 1707T>del (*6) 1707T>del (*6)	Slower conversion to O- and N-demethyltramadol
Methadone	CYP2D6	G 1846A (*4) 1707T>del (*6)	Slower metabolic clearance (although not consistently)
Celecoxib, naproxen, piroxicam, ibuprofen, flurbiprofen	CYP2C9	Al 075C (*3)	Slower metabolism
Acetaminophen	CYP2E1	c2	Accelerated elimination rate
Acetaminophen	Tumour necrosis factor	B2	Lower risk of encephalopathy in patients with acetaminophen-induced acute liver failure
Various NSAIDs	HI-A-DRBI	*11	Higher risk of anaphylactoid reaction

Table 3 Selected pharmacogenetic variants affecting anaesthetic drugs.

Conclusions

In neonates, infants, and children, determining the correct dose for safe and effective treatment remains an immense challenge. The developmental aspects make dosing in the paediatric population difficult by simply scaling adult doses. Distinctive and rapidly varying physiological characteristics contribute to unpredictable dose-exposure responses in children. An understanding and consideration of the developmental aspects in both pharmacokinetics and pharmacodynamics are essential. Fortunately, innovative analytical techniques such as population-based pharmacokinetic analyses and sparse sampling will continue to define doses and maximize efficacy and safety.

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Notes

The Physiology of Venous Circulation

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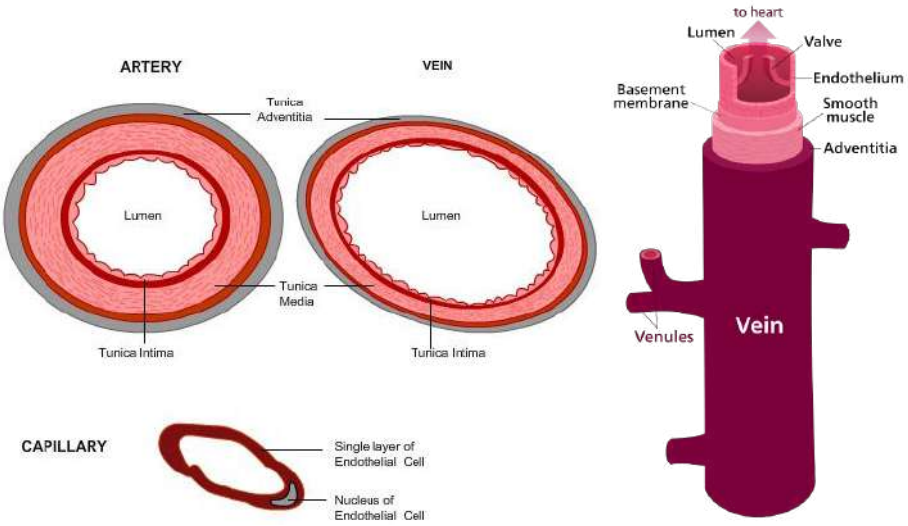
Introduction

Understanding of the complexity of the cardiovascular system is incomplete without knowledge of the venous system.

Blood flow within the body occurs essentially in a closed system so that changes in one system (venous) will have a direct and indirect effect on other components (heart, arteries and capillaries beds). In steady state conditions, blood delivered by the venous system to the heart (venous return) has to equal cardiac output i.e., the heart cannot pump more blood than is delivered to it. Veins are also referred to as ***capacitance vessels*** because they are able to accommodate large volumes of blood. At rest, venous structures contain as much as 70% of blood volume and thus act as a ***blood reservoir***.

The venous system contributes passively and actively to the ***distribution*** of blood between the periphery and heart, influencing right heart ***filling pressure,*** equivalent to ***central venous pressure*** (CVP). It responds rapidly - by transferring blood into or out of the active circulation - to changes in cardiac output, arterial inflow, venous transmural pressure and changes in total blood volume. Stroke volume (SV) is exquisitely sensitive to changes in filling pressure. A 1 cmH_2O change in filling pressure can change SV as much as 50%.
Overview of the anatomy of veins



Veins have a decreased wall thickness to lumen ratio. The tunica intima, media and adventitia are thinner than in arteries with the tunica media containing more collagen but less elastic tissue. This anatomical difference is reflected in the increased compliance of veins compared to arteries (up to 30X more compliant) and the fact that pulsatile flow plays no role in the flow of blood within the venous system (figure 1).

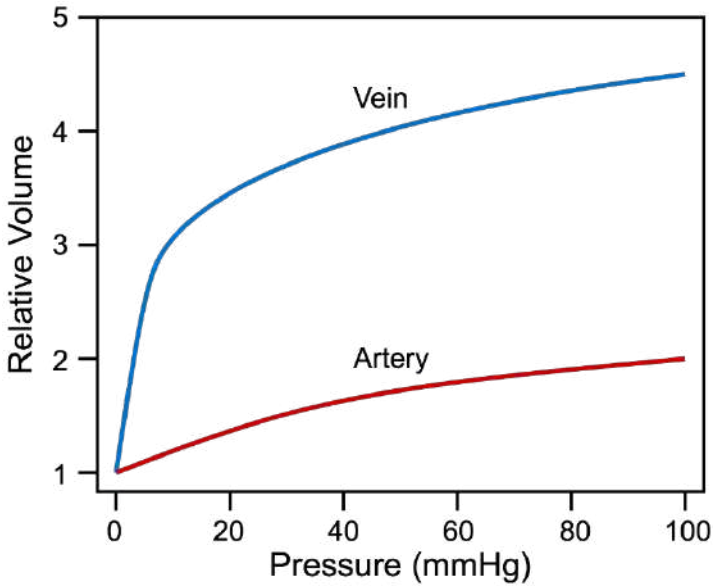


Figure 1

A system of valves ensures that, when competent, flow within the venous system is unidirectional. Below is a list of veins that ***do not*** contain luminal valves:

- Brachio-chephalic veins
- Dural venous sinuses
- The portal venous system
- Superior vena cava
- The thebesian veins
- Vertebral venous plexuses

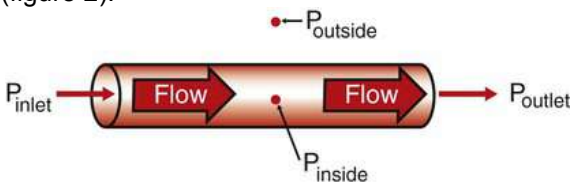
Definitions and basic concepts

Venous Capacity refers to the total volume contained in the vasculature at a given transmural or distending pressure***. Venous compliance*** is a change in volume (∆V) within a vein or venous system associated with a change in distending pressure (∆P).

Venous compliance= ∆V/∆P

Splanchnic and cutaneous veins are the most compliant and represent the largest blood volume reservoirs in the human body. Liver sinusoidal veins as well as the splenic venous system also contribute to reserves but to a much smaller degree. Splanchnic and cutaneous veins are well innervated by α_1 and α_2-adrenergic receptors in contrast to skeletal muscle veins. As the cutaneous circulation is mainly regulated by changes in temperature, venoconstriction and the mobilization of blood volume is mainly limited to the splanchnic circulation.

Transmural pressure is defined as the pressure gradient across a vessel wall. This pressure determines the state of distension of the vessel and is directly related to the volume of blood in its lumen independent of flow (figure 2).



Perfusion pressure = (P_{inlet} – P_{outlet})

Transmural pressure = (P_{inside} – $P_{outside}$)

Figure 2

Unlike arteries and arterioles, veins and venules are thin walled tubes that are 'structurally non-supporting' meaning that when the pressure inside equals the pressure outside, i.e. when the transmural pressure is zero, the cross section does not remain cylindrical as in more rigid vessels but flattens to an approximately elliptical configuration (figure 3).

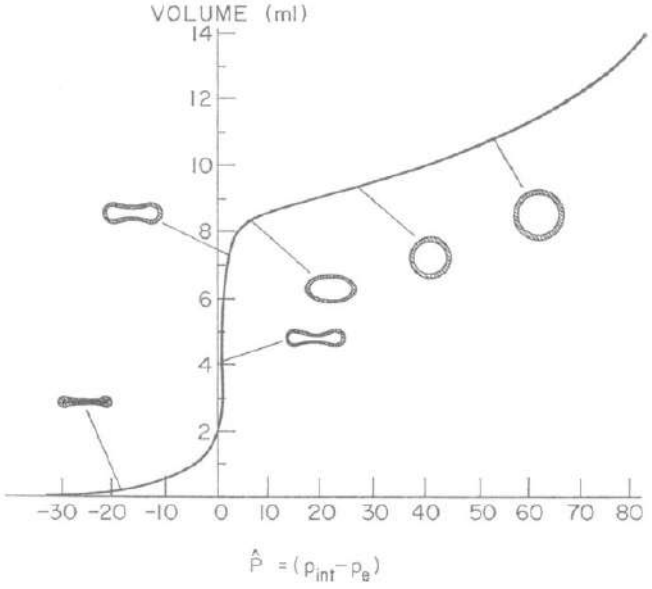


Figure 3

The graph above illustrates this concept. Note that small changes in transmural pressure result in relatively large changes in volume from an elliptical or 'collapsed' configuration to a cylindrical configuration. Once the vessel's cross-section is cylindrical, considerably larger changes in pressure are required to effect a relatively modest increase in volume.

At a transmural pressure of zero, the venous system is at a high distensibility potential but not completely collapsed. This is because even when there is no pressure difference between the inside of the vessel and the surrounding tissues, there is still a considerable amount of blood volume in the system. This blood volume is referred to as ***unstressed volume***. The volume of blood needed to be removed from the capacitance system to decrease its transmural pressure to zero is referred to as ***stressed volume***. The sum of stressed (about 30% of total volume) and unstressed volumes (approximately 70%) is the total volume of blood in the venous system.

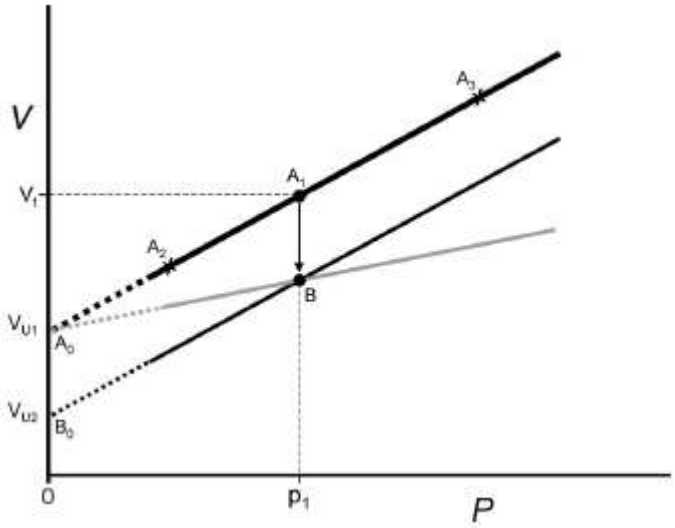


Figure 4

In the graph above (figure 4), **A_1** on the thick black compliance line represents the total blood volume (**V_t**) in veins at a transmural pressure **P_1**. **A_2** and **A_3** represent a change in volume with a change in pressure within the system. Point **A_0** represents the unstressed volume (**V_U**) at zero pressure and the

difference V_t-V_{u1} represents the stressed volume (V_s). Point **B** on the thin black compliance line represents the movement of blood out of the venous reservoir reducing capacity but without a change in compliance. In this instance, V_{u2} represents the new unstressed volume at pint B_0. The grey line represents active mobilization of blood by a decrease in compliance (activation of neuro-hormonal mechanisms increasing vasomotor tone) rather than a decrease in V_u.

Vs determines the ***mean circulatory filling pressure*** (MCFP). This pressure is referred to as the "pivoting pressure" and is the main driving force determining ***venous return*** (VR) to the heart and thus ***cardiac output*** (CO). MCFP is the pressure in the circulatory system when the heart is stopped and no flow occurs. CVP is the pressure of blood in the thoracic vena cava near the right atrium and is an approximation of ***right atrial pressure*** (RAP).

VR = (MCFP – CVP)/Venous resistance

MCFP is approximately between 7 and 12 mmHg (1 mmHg is equivalent to 1.36 cm H_2O) and CVP approximately 0 mmHg with a range of between + 2-3 mmHg and – 3 mmHg.
The gradient for VR is thus between 4 and 10 mmHg and thus a change in CVP of just a few mmHg can have a considerable effect on VR.

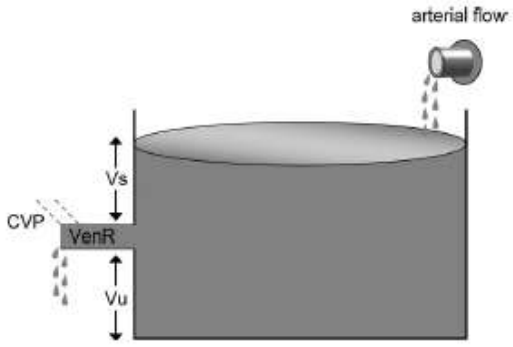


Figure 5

To better understand the relationship between **Vu** and **Vs** a tub analogy is helpful (figure 5). **Vu** is a reserve of blood that can be mobilized into the circulation when needed. A hole between the surface of the water and the bottom divides total blood volume into **Vs** and **Vu.** Water leaves the hole at a rate determined by the diameter of the hole (which reflects venous resistance **VenR**) and the height of the water above the hole, i.e., **Vs.** Water below the hole, equivalent to **Vu,** does not directly participate in the rate of flow of water (VR). Moving the hole down the wall of the tub represents venoconstriction increasing **Vs** in relation to **Vu.** The distal end of the tube attached to the tub represents CVP. The higher the distal end, the higher the CVP and the lower the pressure gradient for venous return and *vice versa.* The tap above the tub represents arterial flow, shown here hydraulically disconnected from the tub due to arterial resistance.

Mechanisms of transfer of blood from the venous reservoir to the circulation

It has already been alluded to that the majority of blood volume in the body is contained in the blood reservoir so described. To all intents and purposes this volume does not participate in the 'functional' circulatory system (heart, arterial system, capillary beds) but is directly affected by changes in that system. A decrease in flow in the arterial system due to an increase in arterial resistance (as a consequence of, for example, hypovolaemia or cardiac failure) leads to a decrease in venous pressure.

To understand how this decrease of venous pressure leads to a shift of blood out of the venous system into the circulation thus increasing in venous return, we must go back to the equation that describes the relationship between compliance, volume and pressure.

Venous compliance= $\Delta V/\Delta P$

Initially, the compliance of the venous system remains the same so a pressure drop will result in a decrease in volume. Because a decrease in flow affects all pressures proportionately, the pressure gradient remains and blood will shift from the venous reservoir to the systemic circulation. Studies have shown that 75% of the volume of blood transferred from the venous system to the systemic

circulation occurs passively, with 25% attributed to active constriction of veins via neuro-hormonal mechanisms. This explains why patients at the beginning of bleeding (up to 10-12% of blood volume) maintain their systemic haemodynamics well without changes in their heart rate, blood pressure or CVP. Decompensation will only occur once the entire VU has been mobilised.

Other factors affecting venous return

Intra-thoracic pressure:

An increase in intra-thoracic pressure during positive pressure ventilation increases intramural CVP which decreases the pressure gradient for VR. However, unless the lung is over-inflated (high inspiratory pressures), excessive PEEP is instituted or there is hypovolaemia, compensatory mechanisms work to maintain VR. Intermittent inflation of the lung increases intra-abdominal pressure as the diaphragm moves downward. This squeezes blood out of the veins within the abdominal cavity increasing MCFP and VR. Reflexes and neurohormonal factors (including the activation of the renin-angiotensin system) also come into play by activating splanchnic arterial and venoconstriction that result in an increase in Vs, maintaining VR and CO.

During spontaneous respiration, intramural CVP decreases leading to an increase in gradient between MCFP and CP facilitating VR. This only functions if CVP is at or above atmospheric pressure as, during inspiration, intra-thoracic veins collapse, preventing a significant increase in VR.
Intra-abdominal pressure.

As described above, diaphragmatic movement during inspiration increases intra-abdominal pressure which shifts blood from the splanchnic system to the systemic circulation. Simultaneously, venous return from the lower limbs is restricted. These cyclical pressure variations do not materially affect VR and CO. However, persistent elevations of intra-abdominal pressure may decrease VR due to an increase in venous resistance. An upward shift of the diaphragm increases intra-thoracic pressure with a concomitant increase in intramural CVP, an elevation that is not in any way a reflection of the patient's volume status and may be associated with a decrease in VR.

Posture:

When standing from a supine position, up to 500 ml of blood can be redistributed to peripheral veins. This is known as "venous pooling". This pooling does not refer to a stagnant reservoir of blood but to blood whose transit time is considerably slowed. This gravity induced venous blood redistribution leads to an immediate drop in stroke volume of up to 40% and a reduction of CO of up to 20%. In healthy individuals compensatory mechanisms are rapidly mobilised, mitigating the effect of blood redistribution and promptly returning blood pressure, CO and CVP to normal values. These compensatory mechanisms are mainly mediated by the sympathetic and renin-angiotensin systems backed by the existence of the 'muscle pump' and venous valves. In instances where these compensatory mechanisms fail, the patient is hypovolaemic or under the effect of anaesthetic agents, venous pooling rapidly decreases VR, CO and ultimately CO, compromising perfusion to the brain and other vital organs.

Pressure in the veins is dependent on the position of the vein in relation to the heart (figure 6). When the venous valves close to prevent retrograde flow, a column of blood extends from the heart to the limbs. The weight of this blood exerts a ***hydrostatic pressure.*** This hydrostatic pressure is referenced to the right atrial pressure (RAP). The greater the distance below the right atrium, the longer the column of blood and thus the higher the pressure.

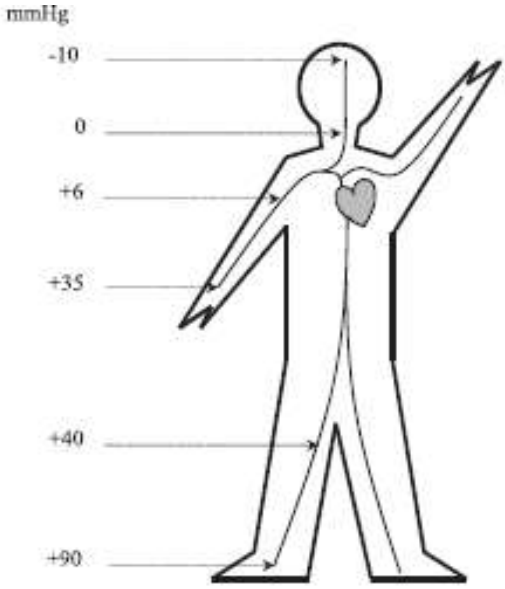


Figure 6

The muscle pump consists of veins that run between skeletal muscles particularly in the lower limbs. Contraction of skeletal muscles surrounding veins increases their luminal pressure which opens venous valves and allows the blood to flow against gravity. When the muscles relax, valves close preventing back-flow of blood. In an individual standing still, the pressure in the veins at the level of the feet can be as high as 90 mmHg but when walking around, this pressure is reduced to as low as 20 mmHg. In this way, venous pooling is limited and the blood is "pumped" back to the heart.

Veins above heart level experience negative hydrostatic pressure. These veins easily collapse during inspiration if intra-thoracic pressure decreases below the pressure of the tissues surrounding the veins. Note that dural sinuses the cranium have rigid walls and do not collapse and so the pressure within them is sub-atmospheric.

Role of reflexes:

Many different pathophysiologic insults (blood loss, upright position, initiation of IPPV) are associated with immediate sympathetic discharge leading to an increase in arterial resistance, heart rate, myocardial contractility and a decrease in venous capacity. Capacitance vessels respond much earlier than resistance vessels to a reduction in blood volume. When the carotid sinus and aortic baroreceptors detect a decrease in blood pressure, sympathetic tone increases, splanchnic veins constrict and Vs and MCFP increase resulting in a shift of blood that maintain venous return to the heart. This response is mediated predominantly by α-adrenergic stimulation.

The significance of central venous pressure

Values of CVP depend on the relation between cardiac pump function and VR which is determined by MCFP, Vs, venous resistance and other factors. However, CVP has been shown to ***not correlate*** with measured circulating blood volume or with responsiveness to fluid challenge. Dramatic changes in systemic haemodynamics, for example, during high thoraco-cervical and general anaesthesia, or a significant decrease in arterial resistance and increase in CO induced by an infusion of prostaglandin E_1 were not associated with any significant or proportional changes in CVP. A correlation between CVP and circulating blood volume does not exist. The reality is that homeostatic mechanisms already alluded to work to maintain transmural CVP at all costs in order to maintain CO in the face of changing circulating blood volume. In fact, the only way to truly measure blood volume is by measuring MCFP which cannot be measured in a clinical setting.

Factors affecting CVP:

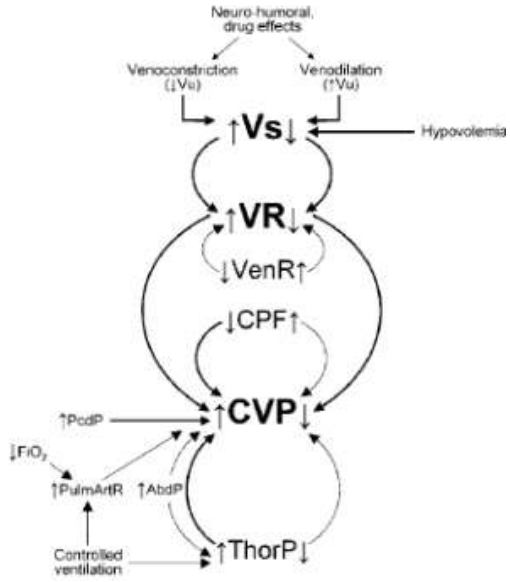


Figure 7

CPF=cardiac pump function; PcdP= pericardial pressure; AbdP= abdominal pressure; VenR= venous resistance; PulmArtR= pulmonary arterial resistance; ThorP= intrathoracic pressure
*** Thickness of the arrows reflects the importance and/or relative frequency of influences in clinical practice**

The main variable that leads to a decrease in CVP is a decrease in Vs (figure 7). Initially, as Vs decreases, blood is shifted from Vu to Vs and CVP is maintained, but when Vu is exhausted Vs begins to decrease and so does CVP. Venodilation which, in effect, is an increase in Vu, shifts blood from Vs to Vu leading to a decrease in Vs by increasing the size of Vu. An isolated increase in venous resistance decreases CVP by a reduction in VR. During forceful inspiration, negative thoracic pressures collapse large veins as they enter the thorax (waterfall effect) which variably decreases VR (depending on volume status) and thus CVP. If CVP decreases are observed, it is likely that there has been blood volume loss in excess of 10-12% or significant venodilation with sequestration of blood within the splanchnic veins.

The main factors that increase CVP other than hypervolaemia are a decrease in cardiac pump function due to any cause. Increased intrathoracic pressure during IPPV with PEEP increases intramural CVP but not transmual pressures. IPPV. An increase in arterial resistance, caused either by mechanical ventilation of by hypoxic pulmonary vasoconstriction increases both intra and transmural CVP.

Potential misrepresentation of a normal central venous pressure

A loss of 10-12% of blood volume does not decrease CVP. Normal CVP may reflect normovolaemia or a compensated hypovolaemia (up to 600-700 ml of blood loss). A combination of factors that have a tendency to decrease or increase CVP may lead to a normal value of CVP despite serious haemodynamic derangements, e.g., the combination of heart failure and hypovolaemia or hypovolaemia in the trendelenberg position. It is only when homeostatic mechanism fail to maintain CVP and thus CO, i.e. in the extremes of haemodynamic derangement that CVP may be a useful indicator of the haemodynamic state of a patient.

Dynamic variables that reflect volume status

It is beyond the scope of this lecture to describe in detail the dynamic variables and its monitoring modalities that are useful in deducing a patient's fluid status. Variables such as pulse and systolic pressure variations, respiratory variations in plethysmographic waveform amplitude and CVP or CO responses to fluid challenges are better indicators of volume status than static haemodynamic variables including CVP. Critical analysis of the literature confirms that in inspiratory decrease in CVP exceeding 1 mmHg is a much better predictor of responsiveness of CO to fluid challenge than CVP *per se.*

Notes

Ventilation Perfusion Interplay

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Driving question:

How does oxygen get to the human cell?

The cardio-respiratory system is responsible for the maintenance of adequate oxygen delivery (DO_2) to the cells to meet their ongoing demand during health and disease. Under normal conditions, the metabolic rate of cells controls DO_2, therefore it is a demand driven process. Oxygen moves down a partial pressure gradient from the atmosphere through the respiratory tract, alveolar gas, arterial blood and systemic capillaries into the cell. It reaches its lowest level inside the mitochondrion where it is utilized. This gradient is called the Oxygen Cascade. DO_2 involves the following steps:

1. Oxygen is taken up from the atmosphere by alveolar ventilation and diffuses from the alveolus to the capillary blood.

2. In the capillary blood oxygen binds to hemoglobin and to a much lesser extent dissolves in the plasma.

3. Through the cardiac output oxygen is transported to the systemic circulation and ultimately delivered into the microcirculation.

4. The oxygen is now released from the hemoglobin and diffuses from the intravascular space into the cells, where it is utilized to maintain cellular function.

The different steps can be broken down to several detailed processes. Some will be discussed below. A good understanding of the physiology of these processes can help to understand human physiology under anaesthesia conditions and treat problems in critically ill patients.

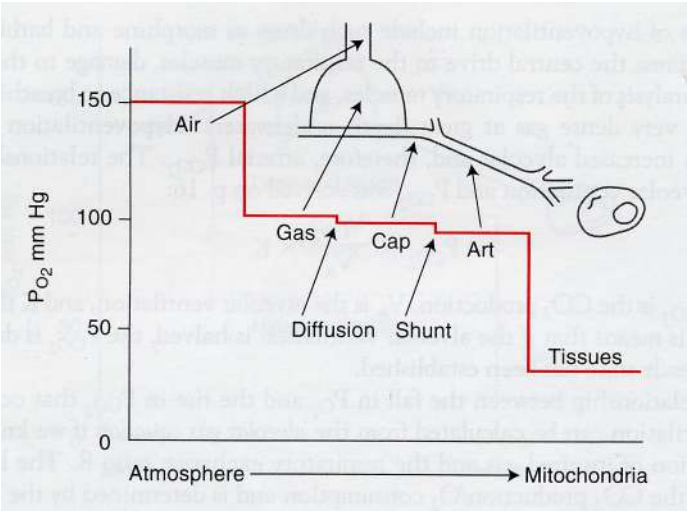

Fig 1. Oxygen Cascade. JB West: Ventilation/Blood Flow and Gas Exchange, ed 4. Oxford, Blackwell, 1985

Ventilation

During inspiration, the diaphragm muscle contracts, which causes it to descend, and at the same time the intercostal muscles raise the ribs. This leads to an increase in the volume of the thoracic cavity and a slightly negative alveolar pressure, which is the main driving force for the flux of air into the lung. Air flows down the trachea and conducting airways into the respiratory zone. The minute volume is the total volume of gas leaving the lung each minute. Not all the air that is inhaled each minute reaches the respiratory zone. About 30% of each breath stays behind in anatomical dead space. The dead space fraction of each breath in a normal individual is therefore around 0.3. The volume that does get in contact with alveoli each minute is called the alveolar ventilation. Tidal volume (VT) is the sum of dead space ventilation (VD) and alveolar ventilation (VA).

$$VT=VD+VA$$

Because all the expired CO_2 in a normal person comes from alveolar gas, VA and PCO_2 are inversely related. Usually the PCO_2 in alveolar gas ($PACO_2$) and arterial blood ($PaCO_2$) is almost identical; therefore alveolar ventilation can be expressed through the following equation:

$$VA=VCO_2/PaCO_2 \times K$$

VCO_2 is the CO_2 production and K is a constant.

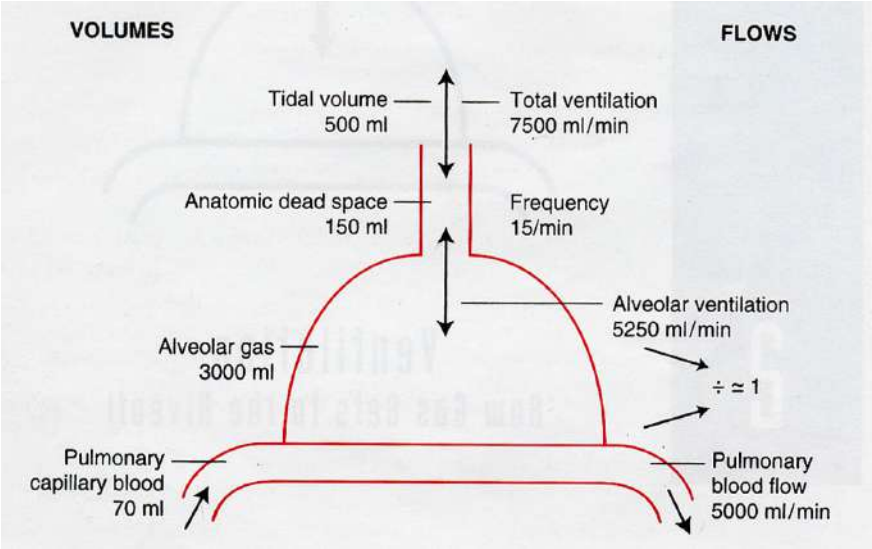

Fig 2. The lung with typical volumes and flows. These values do vary considerably. JB West: Ventilation/Blood Flow and Gas Exchange, ed 4. Oxford, Blackwell, 1985

Alveolar Gas

The fraction of O_2 in air is 20.93%. At sea level barometric pressure is 760 mmHg. As gas is inhaled through the respiratory tract, it becomes humidified. At a body temperature of 37degrees Celsius, water vapor pressure of moist inspired gas is 47 mmHg, therefore the PO_2 of inspired air (PiO_2) can be calculated as follows:

$$PiO_2 = FiO_2 \text{ X } (PB - PH_2O)$$

$$PiO_2 = 20.93/100 \text{ X } (760 - 47) = 149 \text{ mmHg}$$

When O2 has reached alveoli, the PO_2 has fallen to about 100 mmHg, which is by about one-third. This is because a balance between two processes determines the PO_2 of alveolar gas:

- Removal of O_2 by pulmonary capillary blood
- Continuous replenishment of O_2 by alveolar ventilation

Removal of O_2 from the lung is determined by tissue O_2 consumption and does not vary much under resting conditions. Alveolar ventilation (VA) therefore mainly determines alveolar PO_2 (PAO_2).

PAO_2 can be calculated with the Alveolar Gas Equation:

$$PAO_2 = PiO_2 - PACO_2/R + F$$

Where F is a small correction fraction and $R = VCO_2/VO_2$, also called respiratory quotient, with normal value of 0.8.

From the above equation it is easy to understand how a hypoxic gas mixture (FiO_2 less than 21%) or height above sea level (decreased PB) can compromise PAO_2. Hypoventilation also reduces alveolar and arterial PO_2, except when a person breathes an enriched O_2 mixture (increased FiO_2).

Dead space (V_D/V_T)

Dead space ventilation is gas, which participates in ventilation without any matching blood flow. Therefore it does not contribute to gas exchange across the alveolar membrane. Dead space consists of both anatomical dead space and physiological dead space.

Anatomical dead space can be measured using the “nitrogen washout technique of Fowler”. In clinical practice this is not commonly used.

Physiological dead space is easy to use in clinical practice and can be calculated using the Bohr Equation. It measures the volume of lung which does not eliminate CO_2:

$$V_D/V_T = \frac{PaCO_2 - P_ECO_2}{PaCO_2}$$

V_D = physiological dead space, V_T = tidal volume, P_ECO_2 = partial pressure of mixed expired CO_2, $PaCO_2$ = partial pressure of arterial CO_2

Diffusion

Transfer of gas across the blood-gas barrier of the alveolar membrane is called diffusion. This is well described by Fick's Law of Diffusion, which states that the rate of transfer of a gas through a sheet of tissue is proportional to tissue area (A) and difference in gas partial pressures between the two sides (P_1-P_2), and inversely proportional to tissue thickness (T). The area of blood-gas barrier in the lung is enormous and the alveolar membrane is very thin, therefore ideal for diffusion. The rate of gas transfer is also proportional to a diffusion constant, which involves solubility of the gas (sol) and the square root of that gas’ molecular weight (mw).

$$Vgas \quad A/T \times D \times (P_1-P_2) \qquad D = sol/\sqrt{mw}$$

PAO_2 is the driving force (P_1) behind diffusion of O_2 across the alveolar membrane into pulmonary capillaries. In the capillaries O_2 combines with hemoglobin in red blood cells. When haemoglobin is saturated with O_2, the partial pressure of oxygen in pulmonary capillary blood (PcO_2) will start to rise. Under normal resting conditions PcO_2 will almost reach that of alveolar gas (PAO_2) when the red cell is about one-third of the way along the capillary.

Therefore O_2 uptake can be regarded as occurring in two stages:

- Diffusion of O_2 through the blood-gas barrier including plasma and red cell interior.
- Reaction of O_2 with haemoglobin

Resistance to this reaction can be described by the following reaction:

$$1/DL = 1/DM + 1/q \times Vc$$

DL is diffusing capacity of the lung, 1/DM is resistance of the blood-gas barrier, q is the rate of O_2 reaction with haemoglobin and Vc is the volume of pulmonary capillary blood.

In a perfect lung the PO_2 of arterial blood would be the same as that of alveolar gas. In real life this is not true. As blood travels through the pulmonary capillary, its PO_2 rises closer and closer to that of alveolar gas. Under normal conditions there is a small difference between alveolar and end-capillary PO_2, because of incomplete diffusion.

Pulmonary circulation/Perfusion

Pulmonary vascular circulation is a low-resistance network in series with the systemic circulation. The pulmonary arterial pressure is about one-sixth of the systemic arterial pressure. Calculating pulmonary vascular resistance (PVR) using Ohm's Law of Resistance:

$$\text{PVR} = \frac{\text{MPAP} - \text{PCWP}}{\text{CO}} \times 80 \text{ dynes.s cm}^{-5}$$

The normal PVR ranges from 90 to 150 dynes.s.cm−5. Cardiac output (CO), mean pulmonary artery pressure (mPAP) and pulmonary capillary wedge pressure (PCWP) have to be obtained with a Pulmonary Artery Catheter (PAC) to calculate PVR.

The volume of blood in the pulmonary circulation is around 500 ml. This varies during physiological changes in blood distribution e.g. standing upright, lying down, Valsalva manoeuver, etc.

Since the systolic pulmonary arterial pressure is so low (sPAP less than 20 mmHg), both pulmonary flow and pressures are influenced by gravity. At rest, in the upright position, there is less flow to the lung apices, with greatest flow to the lung bases. The pulmonary capillary pressure is around 10 mmHg, considerably lower than the plasma colloid osmotic pressure. However, because tissue protein concentration is high in lung tissue, some filtration does take place leading to lymph formation.

Ventilation-Perfusion interplay

In an ideal lung unit, ventilation and perfusion will be perfectly matched with ventilation-perfusion ratio of 1:1.

Unfortunately this is not possible due to various reasons. Regional differences due to gravity and other factors lead to ventilation-perfusion mismatch in many alveolar units. Uneven distribution of blood flow to the lungs is partly offset by a similar distribution of ventilation. The alveolar excursion during ventilation is more in the dependent sections of the normal lung due to the weight of upper lobes (non-dependent zones/West Zones 1 and 2) lying on the dependent lung (West Zone 3). Therefore both perfusion and ventilation are happening to a larger extent in the base (dependent zones/West Zone 3) of the lung, perfusion more so than ventilation. This depends on the intravascular perfusion pressure and blood volume. It become clinically important in critically ill patients e.g. hypovolemic shock, hypovolemic critical care patient with high ventilation driving pressure and on high PEEP, etc. It is also clinically visible when separating a cardiac patient from cardiopulmonary bypass support.

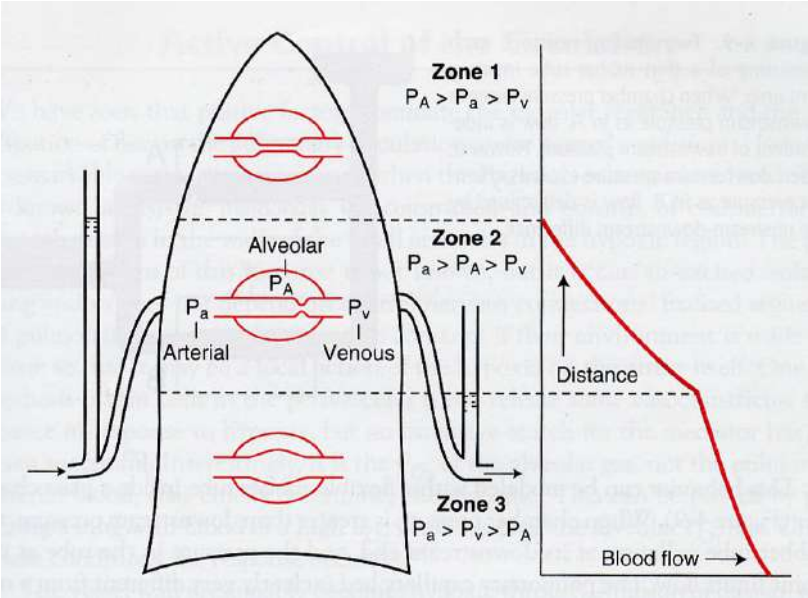

Fig 3. The "West Zones". Uneven distribution of blood flow through the lung.
JB West et al. J Appl Physiol 1964;19:713.

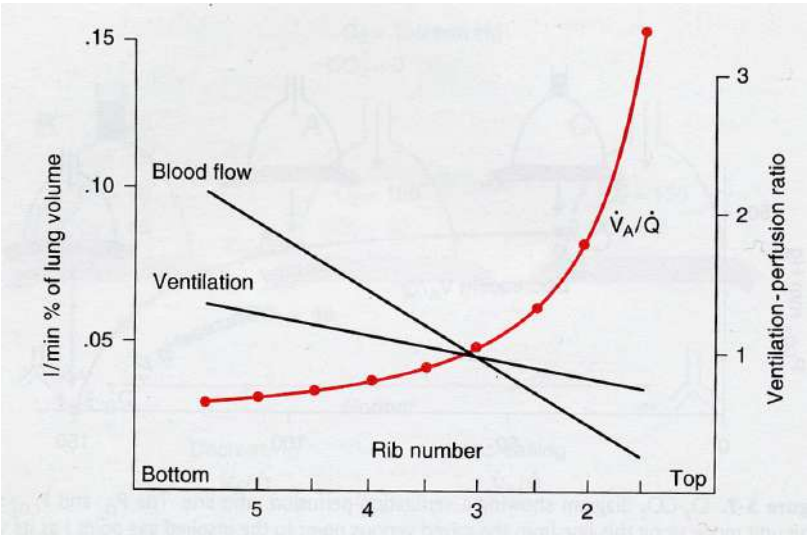

Fig 4. Distribution of ventilation and perfusion from the bottom to the top of the lung. JB West: Ventilation/Blood Flow and Gas Exchange, ed 4. Oxford, Blackwell, 1985

Shunt (Q_S/Q_T)

The reason why PaO_2 is less than PAO_2 is the fraction of shunted blood. Shunt refers to blood that enters the arterial system without going through ventilated areas of lung. In a normal person, blood that has perfused the bronchi and lung tissue is partially depleted of O_2 and drains through bronchial arteries via the pulmonary veins into the left atrium. Also, blood that has perfused the myocardium drains through Thebesian veins directly into the cavity of the left side of the heart. The effect of adding these poorly oxygenated blood components to the well-oxygenated blood coming from the lungs via the pulmonary veins, is to depress the systemic PaO_2. This leads to a normal anatomical shunt of about 1-2%.

Respiratory pathological shunt (low V/Qs) refers to blood that enters the left side of the heart without flowing past ventilated alveoli, such as occurs in areas of atelectasis, consolidation-pneumonia or alveolar oedema.

The amount of shunt can be calculated. The total amount of O_2 leaving the system is total blood flow

QT, multiplied by O_2 concentration in the arterial blood (CaO_2), or Q_T X CaO_2. This must equal the sum of the amounts of O_2 in shunted blood, Q_S X CvO_2, and end-capillary blood, (Q_T-Q_S) X CcO_2. Therefore:

$$Q_T \text{ X } CaO_2 = (Q_S \text{ X } CvO_2) + (Q_T - Q_S) \text{ X } CcO_2$$

Rearranging this gives

$$Q_S/Q_T \text{ (shunt fraction)} = CcO_2 - CaO_2/CcO_2 - CvO_2$$

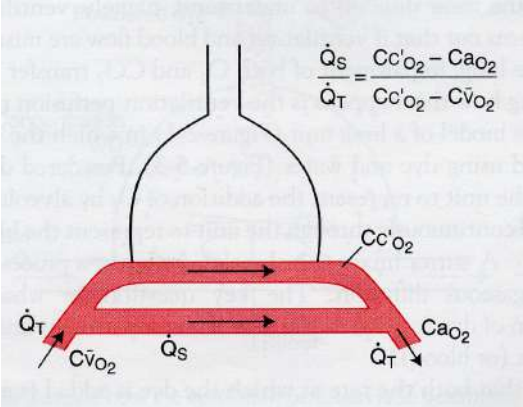

Fig 5. Calculating shunt flow. JB West: Ventilation/Blood Flow and Gas Exchange, ed 4. Oxford, Blackwell, 1985

In patients with a congenital defect/hole between the right and left sides of the heart there may be right to left flow (e.g. ASD or VSD with increased pulmonary pressures/ Eisenmenger syndrome), with direct addition of venous deoxygenated blood to arterial oxygenated blood coming from the lungs into the left ventricle. This truly pathological shunt refers to blood that has passed from right to left through this defect without exposure to oxygen exchange in the lung. This will also lead to a decreased PaO_2.

In the presence of such an ASD or VSD, one can use the flow ratio between pulmonary and systemic circulations to indicate the magnitude of shunt. Systemic blood flow (Qs) can be calculated from the left ventricular outflow tract (LVOT) and pulmonary blood flow (Qp) from the right ventricular outflow tract (RVOT).

Qp = RVOT cross sectional area (cm^2) x RVOT velocity time integral (cm)
Qs = LVOT cross sectional area (cm^2) x LVOT velocity time integral (cm)

The cross sectional areas of, and flow velocity across the RVOT and the LVOT are determined with 2D and Doppler echocardiography:

$$\text{Cross sectional area} = \frac{(\text{diameter})^2}{2} \times \pi$$

The velocity time integral (VTI) is equal to the distance (cm) blood travels with each beat of the heart and is measured with pulsed wave Doppler. In a normal individual the VTI_{RVOT} should be equivalent to VTI_{LVOT}.

Usually an ASD will have a left to right shunt until the longstanding increased pulmonary blood flow leads to vascular changes in the pulmonary bed with subsequent pulmonary hypertension and reversal of flow from right to left.

A left to right shunt will be considered severe when the Qp/Qs ratio is more than 2/1. On the other hand, a patient with significant right to left shunting will have a Qp/Qs ratio of less than 1/2 which means that half of the cardiac output would bypass the pulmonary circulation and that blood would not be oxygenated. This is the basis of hypoxaemia in cyanotic heart disease.

Shunt does not result in hypercarbia because chemoreceptors recognize any increase in $PaCO_2$ and the body responds by increasing ventilation.

Shunt and dead space are on two ends of a spectrum.
Dead space ventilation and high V/Q alveolar units lead to hypercarbia.
Shunt flow and low V/Q alveolar units lead to hypoxia.

Ventilation-Perfusion mismatch

The lung consists of:

- Alveoli which are ideally ventilated and perfused.
- Alveoli which are perfused but not well ventilated (low V/Qs or shunt).
- Alveoli which are ventilated but not perfused (high V/Qs or dead space).

The top of the lung (West Zones 1-2) with relatively "over-ventilated" and "under-perfused" alveoli contributes more to dead space ventilation and hypercarbia. The base, more dependent part of the lung (West Zone 3) with relatively over-perfused and under-ventilated alveoli, contributes more to shunt and hypoxaemia.

The ventilation-perfusion ratio of each alveolar unit can vary from zero (no ventilation = shunt leading to hypoxaemia), to infinity (no perfusion = dead space resulting in hypercarbia). In-between exist alveoli on a spectrum range of high- to low- ventilation-perfusion matching.

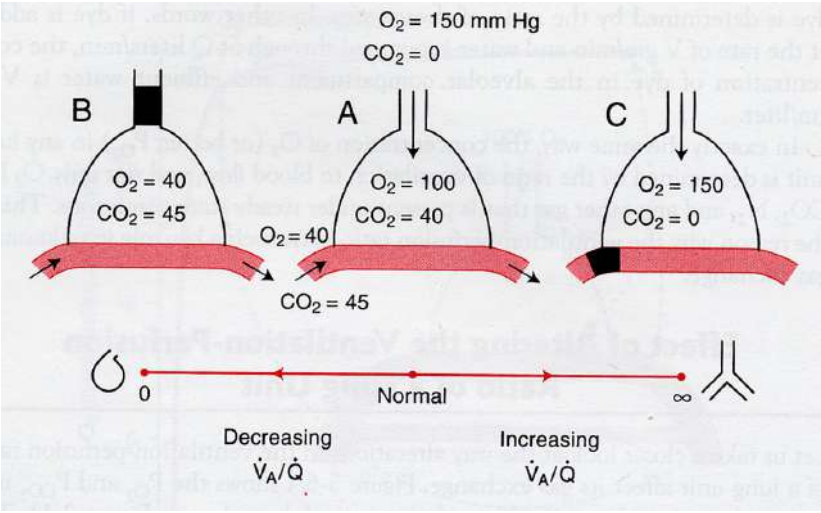

Fig 6. The spectrum of ventilation-perfusion matching from low to high. JB West: Ventilation/Blood Flow and Gas Exchange, ed 4. Oxford, Blackwell, 1985

Normal anatomical/physiological shunt seldom causes hypoxaemia. Usually hypoxaemia is caused by ventilation-perfusion mismatch with predominantly low V/Q relationships. In hypoxaemia caused by a true congenital shunt, increasing the FiO_2 makes little difference to its severity. However, in the presence of low V/Q relationships, an increase in FiO_2 will improve the PaO_2.

The venous admixture (Q_{VA}) of all different alveolar units and compositions of blood flowing through the 4 pulmonary veins back into the left atrium, leads to a sum decrease in PaO_2 (arterial).

The PAO_2-PaO_2 gradient (A-a gradient) can be used as an index of ventilation perfusion mismatch. In a healthy, young person on room air the normal A-a gradient is less than 10 mmHg. It increases with age and with lung pathology, which impairs gas exchange.

Influences on pulmonary vascular resistance (PVR)

Unlike certain specialized regions of the systemic circulation, pulmonary blood flow is not auto-regulated but depends on systemic blood flow. During exercise or disease, pulmonary blood flow can increase up to five-fold, with only a minor increase in pulmonary arterial pressure. This is partly because of the distensibility of the pulmonary vasculature and partly because a minor increase in pressures leads to an increase of blood flow to the apices of the lung (West Zones 1 and 2).

Although to a much lesser extent than systemic vessels, pulmonary arterioles and capillaries contain some smooth muscle with sympathetic innervation. Stimulation of peripheral chemoreceptors results in pulmonary vasoconstriction. Hypercarbia as well as hypoxia increase pulmonary vascular resistance through a direct effect on the circulation. It therefore can lead to pulmonary hypertension and even pulmonary oedema. This is the opposite of what happens in the systemic circulation where hypercarbia and hypoxaemia lead to vasodilatation.

In the lung, localized alveolar hypoxia in specific regions leads to capillary vasoconstriction to those alveoli. Blood flow is directed away from the hypoxic alveoli to units with adequate alveolar ventilation. This physiological safety reflex is called hypoxic pulmonary vasoconstriction (HPV). HPV is active already in utero, reducing pulmonary blood flow, and in adults helps to match regional ventilation and perfusion, although it has little effect in healthy lungs. Important to recognize that this strong reflex occurs due to hypoxia in a specific alveolus and region, as is the case in lung sections with regional atelectasis or alveolar oedema. The ref!ex is biphasic. Once the second phase becomes active after about an hour of alveolar hypoxia, the pulmonary vasoconstriction may take hours to reverse after normoxia returns.

Driving questions for next time:

What are the respiratory causes of hypoxemia?

Decreased FiO_2
Hypoventilation
Shunt
Low V/Q and Diffusion abnormalities
Impaired cardiac output causing poor DO_2 in the presence of low V/Qs

How does oxygen get to the human cell when the lungs are broken?

Conclusion

Many factors are involved in the process of tissue oxygen delivery. Good knowledge of the physiological processes involved can help to understand the pathophysiology of tissue hypoxia and its treatment.

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Notes

Single Best Answer (SBA) Practice Questions

Contributors:

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1. PHYSICS

Humidification

Question 1.1

Requirement for energy during humidification in a human

Which statement describes the energy requirements for the humidification of breath in humans most accurately?

a. Energy is required to turn the kinetic energy of water molecules breathed, into static energy.
b. When energy is released during the process of humidification, it is used to warm the air breathed.
c. The energy required to humidify the air breathed is more than the energy required to heat the air.
d. The energy required to humidify the air breathed has similar impact in an infant when compared to an adult.

Question 1.2

How can the humidity of gasses supplied by a circle breathing system be increased?

a. Decrease the fresh gas flow.
b. Decrease dead space by removing the HMEF.
c. Exclude the soda lime from the system.
d. Disconnect the scavenging from the wall inlet.

Question 1.3

Which of the following is a complication of inhalation of dry gas directly into the trachea?

a. Increased mucociliary clearance.
b. Increased atelectasis.
c. Increased flow rate during exhalation.
d. Increased body temperature.

Question 1.4

Choose the correct definition for humidity:

a. Absolute humidity is the volume of water in a given volume of gas.
b. Relative humidity is the amount of water vapour present in a volume of gas as a percentage of the amount of water vapour that is required to fully saturate the same volume of gas.
c. Water vapour pressure is the partial pressure exerted by water vapour in a gas mixture.
d. Dew point is the humidity at which ambient air is fully saturated.

Question 1.5

How may the inclusion of a hot water humidifier in a ventilator circuit affect the compliance of the system?

a. The heated wire will cause the plastic circuit to change pliability, decreasing the compliance of the circuit.
b. Water condensation can trigger the ventilator, causing the ventilator to calculate a lower compliance.
c. Flow through the hot water humidifier will increase resistance in the system, thereby increasing the compliance of the system.
d. Addition of a water bath increases the compression volume of the circuit, increasing the compliance of the circuit.

Lasers, fires and explosions

Question 1.6

A critical feature of laser light includes:

a. Coherence of light
b. Dispersed beam
c. Low power density
d. Wide spectrum of frequency

Question 1.7

A stoichiometric mixture results in:

a. An uncompleted combustion process
b. The least violent reactions
c. No excess reactant being produced
d. Some residual reagent remaining

Question 1.8

The following class of laser includes high-powered lasers that can cause fire:

a. Class I Lasers
b. Class 2 Lasers
c. Class 3 Lasers
d. Class 4 Lasers

Question 1.9

The following agent may increase the risk of fire when used with oxygen:

a. Air
b. Helium
c. Nitrous oxide
d. Xenon

Question 1.10

Carbon dioxide extinguishers should be avoided for what class of fire?

a. Class A (paper, wood, cloth and plastics)
b. Class B (flammable liquids)
c. Class C (electrical equipment)
d. All of the above

Pulse oximeter

Question 1.11

The principle employed in pulse oximetry of passing radiation through a sample and determining the quantity absorbed is known as:

a. Beer's law
b. Lambert's law
c. Plethysmography
d. Spectrophotometry

Question 1.12

The 2 wave pulse oximeter is capable of measuring what kind of haemoglobin?

a. Carboxyhaemoglobin
b. Deoxyhaemoglobin
c. Fetalhaemoglobin
d. Methaemoglobin

Question 1.13

A pulse oximeter reading of 85% is due to:

a. Higher absorbance of light at 660nm than 940nm
b. Isosbestic point
c. Methaemoglobinaemia
d. Red/Infrared light ratio of 0,43

Question 1.14

A 60-year-old female with bowel obstruction, COPD (50 pack year smoking history) and blue nail polish is admitted to PAHCU post-adhesiolysis surgery. The surgeon used methylene blue intra-operatively. On handover the anaesthetist mentions the intra-operative saturation measured via pulse oximetry (SpO_2) was 92%. An arterial blood gas taken at this time and run via a bloodgas analyser with co-oximetry reported a fractional saturation of 85%. This phenomenon could be explained by:

a Blue nail polish
b Carboxyhaemoglobin
c Methaemoglobinaemia
d Methylene blue

Question 1.15

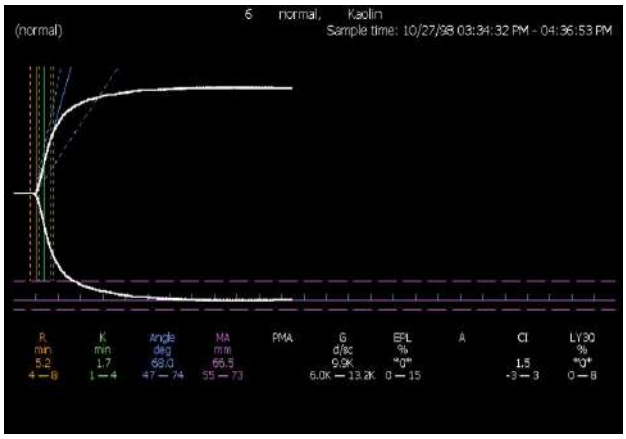
A 65-year-old male with tricuspid valve incompetence is admitted for an elective knee replacement. He is clinically pale, with a ward Hb of 7. A pulse oximeter probe is tightly secured around his finger. The saturation reading is 86%. Clinically he is not distressed with clear lung fields on auscultation. An

arterial blood gas is done which shows SaO_2 of 97%. The low pulse oximeter saturation could be explained by:

a. Anaemia
b. Faulty Sats probe
c. Penumbra effect
d. Venous pulsations

Visco-elastic testing of coagulation

Use the following thromboelastogram (TEG) to assist in answering questions 1.16 to 1.20



Question 1.16

What parameter on a TEG correlates most closely with fibrinogen function?

a. R-time
b. K-time
c. Alpha angle
d. MA

Question 1.17

What is the single parameter that represents overall coagulation status?

a. MA
b. LY30
c. CI
d. EPL

Question 1.18

What would be the most useful indication of TEG in the clinical arena?

a. To detect the risk of bleeding in patients peri-operatively
b. To define the cause of bleeding in trauma patients
c. To limit the use of unnecessary blood products during resuscitation of bleeding patients
d. To detect the presence of hypercoagulability in acutely ill patients

Question 1.19

Which parameter best represents platelet function on a TEG?

a. MA
b. PMA

c. G-value
d. None of the above

Question 1.20

What is the best indicator of fibrinolytic activity on the TEG?

a. EPL
b. LY30
c. CI
d. None of the above

Nitrous Oxide

Question 1.21

Which of the following statements regarding the environmental impact of nitrous oxide is true?

a. Nitrous oxide is a greenhouse gas with global warming potential that is regulated by both the Kyoto protocol and the Montreal protocol.
b. Nitrous oxide is a greenhouse gas with global warming potential that is regulated by the Kyoto protocol but not regulated by the Montreal Protocol.
c. Nitrous oxide is a greenhouse gas with global warming potential that is regulated by the Montreal protocol but not by the Kyoto protocol.
d. Nitrous oxide is a greenhouse gas with global warming potential but as an essential medical gas is unregulated by both the Kyoto and Montreal protocol.

Question 1.22

Entonox is comprised of a 50:50 mixture of oxygen and nitrous oxide and is used as an inhalation analgesic in some labour wards. When under storage as a gas in a cylinder, which of the following is the best way to ensure that the mixture in the cylinder does not undergo lamination?

a. Do not store the cylinder in temperatures below 36.5 degrees Celsius
b. Do not store the Entonox in a cylinder but use pipeline Entonox at 4 bar
c. Do not store the cylinder in temperatures below -6 degrees Celsius at 137 bar
d. The temperature at which Entonox is stored does not matter as long as the pressure in the cylinder is maintained at 137 bar.

Question 1.23

Nitrous oxide is often used in general anaesthesia in conjunction with a volatile agent as they work synergistically to produce amnesia and hypnosis. Which of the following statements regarding its use in routine clinical practice is correct?

a. The use of nitrous oxide during general anaesthesia for Caesarean Section is recommended by the NAP5 audit as nitrous oxide has been shown to decrease the risk of awareness
b. The use of nitrous oxide during general anaesthesia for laparoscopic surgery is recommended by the NAP5 audit as nitrous oxide has been shown to decrease the risk of awareness.
c. Bispectral index (BIS) monitoring should be used to monitor the level of anaesthesia when nitrous oxide is in use.
d. Nitrous oxide inhibits the GABA receptors and therefore has potential in prevention of the development of chronic pain.

Question 1.24

Nitrous oxide is often used during maintenance of anaesthesia due to it's effect on other inhaled gases. Which statement is the most correct?

a. Nitrous oxide can decrease arterial oxygenation due to absorption atelectasis as it is more soluble than nitrogen.
b. Nitrous oxide will increase the amount of volatile required to achieve MAC (minimum alveolar concentration) due to it's additive effects as a hypnotic agent.
c. Nitrous oxide can improve arterial oxygenation due to it's persisting concentrating and second gas effects.
d. Nitrous oxide demonstrates increasing anaesthetic efficiency at increasing altitude.

Question 1.25

The pressure gauge on the nitrous oxide cylinder at the back of your machine reflects that it is full. When the cylinder is opened however the pressure rapidly drops and nears zero. What is the most likely explanation?

a. The pressure gauge on the cylinder is faulty.
b. The cylinder's pressure gauge does not accurately reflect the filling pressure of the cylinder and should therefore be ignored.
c. The pressure on the nitrous oxide gauge is dropping because latent heat of vaporisation is cooling the cylinder, thereby dropping the saturated vapour pressure of the nitrous oxide.
d. The nitrous oxide cylinder is nearing empty.

Solubility

Question 1.26

An important factor contributing to increased solubility of a solute in a solvent in the same state is:

a. adding heat to an exothermic reaction
b. common-ion effect
c. molecular size in gases
d. polarity in liquids

Question 1.27

Ostwald's solubility coefficient is:

a. corrected to standard temperature
b. dependent on Henry's law
c. independent of temperature
d. independent of the pressure of the gas or vapour

Question 1.28

The partition coefficient differs from Ostwald's solubility coefficient because
a. it can be applied to phases other than gas and liquid
b. it cannot be applied to two liquids
c. it is dependent on temperature
d. the relative phase order is not defined

Question 1.29

Potency of a volatile anaesthetic depends on its
a. blood : gas partition coefficient
b. minimum alveolar concentration (MAC) value
c. oil : gas partition coefficient
d. Ostwald's coefficient

Question 1.30

Increased solubility of an anaesthetic agent

a. increases the onset of action of the anaesthetic agent
b. increases the second gas effect of nitrous oxide at induction
c. increases the slope of the F_A/F_i (fraction of alveolar partial pressure to inspired partial pressure of that agent)
d. increases uptake of that anaesthetic agent

Transducers

Question 1.31

The natural frequency of an invasive blood pressure measuring system is determined by the properties of its components. It may be increased by:

a. Increasing the length of the cannula or tubing
b. Increasing the compliance of the cannula or diaphragm
c. Increasing the density of the fluid used in the tubing
d. Increasing the diameter of the cannula or tubing

Question 1.32

Damping occurs when the system absorbs the energy of oscillations, reflected as decreased amplitude. Some degree of damping is required in all systems (critical damping), but if excessive (overdamping) or insufficient (underdamping) the output will be adversely affected. Causes of overdamping include:

a. Short, narrow tubing
b. Non-compliant tubing
c. Three way taps
d. Dextrose – containing fluid

Question 1.33

Overdamping distorts the amplitude excessively, and can result in inaccuracies in measurement of pressure. An overdamped invasive blood pressure measurement system would show:

a. A decreased Diastolic Blood Pressure
b. A decreased Systolic Blood Pressure
c. A decreased Mean Arterial Pressure
d. An increased Systolic Blood Pressure

Question 1.34

You note a significant difference between the invasive blood pressure reading in one arm, and the non-invasive blood pressure reading in the other arm of a patient. What are the possible causes?

a. The transducer system has been set up incorrectly
b. The transducer system was zeroed incorrectly
c. The artery is in spasm
d. All of the above

Question 1.35

The shape of the arterial waveform changes according to the distance of the catheter from the aortic valve. The greater the distance between the catheter and the aorta:

a. The smaller the systolic peak (i.e. a lower systolic pressure)
b. The further the dicrotic notch
c. The higher the end-diastolic pressure (i.e. the narrower the pulse pressure)
d. The earlier the arrival of the pulse

2. PHYSIOLOGY

Insulin

Question: 2.1

In a healthy subject, glucose ingestion will lead to the release of Insulin from pancreatic B cells. Insulin will then enter the circulation and diffuse into its primary target tissues, binding to specialized receptors. Which of the following is example of an endocrine effect of insulin on the liver?

a. Insulin stimulates glycogenolysis
b. Insulin stimulates gluconeogenesis
c. Insulin stimulates protein synthesis
d. Insulin stimulates triglyceride synthesis

Vitamin D

Question 2.2

Pertaining to *the solubility of Vit D and its source*, choose the most correct statement:

a. Is a water-soluble vitamin that is abundantly present in food with dermal synthesis playing a minor role
b. Is a fat-soluble vitamin which is present in very few foods so dermal synthesis is the major natural source
c. Is a water-soluble vitamin that is abundantly present in food with dermal synthesis also acting as a major natural source
d. Is a fat-soluble vitamin which is abundantly present in food with dermal synthesis playing a minor role

Question: 2.3

Concerning the *Chemistry* of Vitamin D choose the most correct statement:

a. Has a 3-carbon glycerol backbone. 1,25- dihydroxyvitamin D is the major circulating form and less potent than 25-hydroxyvitamin D (25[OH]D) the most active form.
b. Has a four-ringed cholesterol backbone 1,25- dihydroxyvitamin D is the major circulating form and less potent than 25-hydroxyvitamin D (25[OH]D) the most active form.
c. Has a four-ringed cholesterol backbone 25-hydroxyvitamin D (25[OH]D) is the major circulating form and less potent than 1,25-dihydroxyvitamin D the most active form.
d. Has a 3-carbon glycerol backbone 25–hydroxylase is the major circulating form and more potent than 1,25-dihydroxyvitamin D the least active form.

Question 2.4

Regarding the *Metabolism* of Vit D choose the most correct statement:

a. Vit D3 undergoes enzymatic conversion in the liver via 25-hydoxylase to 25-hydroxyvitamin D2 (25[OH]D)
b. Vit D3 undergoes enzymatic conversion in the kidney via 25-hydroxylase to 25-hydroxyvitamin D2 (25[OH]D)
c. Vit D3 undergoes enzymatic conversion in the liver via 1-alpha-hydroxylase to 25-hydroxyvitamin D2 (25[OH]D)
d. Vit D3 undergoes enzymatic conversion in the kidney via 25-hydroxylase to 25-hydroxyvitamin D2 (25[OH]D)

Question 2.5

Regarding the *Metabolism* of Vit D choose the most correct statement:

a. Within liver hepatocytes, 25[OH]D is further converted via 1-alpha-hydroxylase to produce the most active form 1,25-dihydroxyvitamin D
b. Within the renal tubular cells, 1,25- dihydroxyvitamin D is further converted via 1-alpha-hydroxylase to produce the most active form 25[OH]D
c. Within the liver hepatocytes, 1,25- dihydroxyvitamin D is further converted via 1-alpha-hydroxylase to produce the most active form 25[OH]D
d. Within the renal tubular cells, 25[OH]D is further converted via 1-alpha-hydroxylase and 24-alpha-hydroxylase to produce the most active form 1,25-dihydroxyvitamin D

Question 2.6

The *active form of Vitamin D* is regulated by:

a. A positive feedback where a rise in plasma calcium causes an increase in PTH that inhibits 1-alpha-hydroxylase
b. A negative feedback where a fall in plasma calcium causes an increase in PTH that stimulates 25-hydoxylase
c. A negative feedback where a fall in plasma calcium causes an increase in PTH that stimulates 1-alpha-hydroxylase
d. A positive feedback where a rise in plasma calcium causes an increase in PTH that inhibits 25-hydroxylase

Physiology of Carbon Dioxide

Question 2.7

Carbon dioxide production occurs in cells. A portion of all carbon dioxide is carried in the blood in solution. Carbon dioxide in solution has the following properties:

a. Carbon dioxide is 20 times more soluble than oxygen and obeys Henry's law.
b. 25% of carbon dioxide is carried in solution in the plasma and 75% in the red blood cell.
c. As body temperature increases, more carbon dioxide can be carried in solution.
d. Carbon dioxide partial pressure of alveolar and end-capillary blood varies greatly.

Question 2.8

Carbon dioxide is produced by cell metabolism in the cytoplasm and mitochondria. It diffuses into the blood and is transported to the lungs. The Hamburger effect describes:

a. The combination of carbon dioxide with water inside the red blood cell to form carbonic acid, which freely dissociates into hydrogen and bicarbonate ions.
b. The diffusion of bicarbonate ions into the red blood cell in exchange for chloride ions.
c. The shift of chloride ions into the red blood cell as blood undergoes the transition from arterial to venous gas partial pressures.
d. The ability of reduced haemoglobin to accept hydrogen ions and thus increase the carbon dioxide content of deoxygenated blood.

Question 2.9

The carbon dioxide dissociation curve differs significantly from the oxygen-haemoglobin dissociation curve. The following are key differences:

a. Between partial pressures of 5 – 6 kPa, the change in concentration of carbon dioxide is smaller than that of oxygen.
b. The carbon dioxide dissociation curve is more linear and much steeper than the oxygen-haemoglobin dissociation curve.
c. At an equivalent partial pressure, the content of oxygen in the blood will be more than that of carbon dioxide.
d. Oxygen-haemoglobin dissociation is affected by carbon dioxide partial pressure. The oxygen content of blood has no effect on the affinity of haemoglobin for carbon dioxide.

Question 2.10

Carbon dioxide is integral to the regulation of gaseous exchange. Regarding the action of carbon dioxide on chemoreceptors:

a. The central and peripheral chemoreceptors are sensitive to changes in P_aO_2, P_aCO_2 and the concentration of hydrogen ions.
b. The principle mechanism increasing the activity of central chemoreceptors in the medulla, is the diffusion of carbon dioxide from surrounding blood vessels into the extracellular fluid.
c. With hypoventilation, the central chemoreceptors will alter ventilation more rapidly in response to a change in arterial pH than cerebrospinal fluid (CSF) pH.
d. Peripheral chemoreceptors are located in the carotid and aortic bodies. An increase in P_aCO_2 increases activity in both, but a fall in pH only affects the carotid bodies.

Question 2.11

Carbon dioxide is an important factor in cerebral vascular regulation. Which statement best describes carbon dioxide's role:

a. The response of the cerebral circulation to changes in P_aCO_2 is independent of resting cerebral blood flow (CBF).
b. Hypotension below the lower limit of autoregulation can abolish the response of CBF to hypocapnia.
c. Acute hypercapnia has little to no effect on cerebral autoregulation.
d. The response of CBF to P_aCO_2 shows little to no change with hypothermia

Intermediary Metabolism

Question 2.12

Regarding intermediary metabolism:

a. It involves the anabolism (breakdown) and catabolism (synthesis) of macromolecules.
b. Cellular energy can only be generated from aerobic oxidation of metabolic fuels (carbohydrates, fats, proteins) derived from an ingested meal and not from stores.
c. In the electron transport chain, electrons are transferred through a series of carriers of lower potential and the energy released during this is used to form ATP. These electrons finally combine with the end electron acceptor carbon dioxide, to form oxygen.
d. Reduced coenzymes (NAD^+ and FADH) are intermediate energy storage compounds that aid electron (and energy) transfer from metabolic reactions (glycolysis and Krebs cycle) to the electron transport chain.

Question 2.13

With respect to lactate metabolism, which statement is false?

a. Hyperlactaemia is variably associated with acidaemia.
b. Ethanol excess produces a Type B lactic acidosis.
c. A proportion of plasma lactate is produced by both erythrocytes and the heart.
d. Lactate is metabolised by the liver, kidneys and skeletal muscle.

Question 2.14

Regarding red blood cell metabolism

a. Aerobic and anaerobic metabolism can take place.
b. The glycolytic pathway produces 36 ATP molecules for each molecule of glucose utilised.
c. Glycolysis directly produces reduced forms of pyridine nucleotides for glutathione reduction, methaemoglobin reduction and to neutralise oxidants that may lead to globin degradation.
d. The Leubering-Rappaport pathway leads to the formation of 2,3 Diphosphoglycerate, which is influenced by general metabolism, thyroid and growth hormonal influence, chronic hypoxaemia or anaemia.

Question 2.15

Concerning cellular metabolism, which statement is false?

a. Glucose is predominantly metabolized via glycolysis, free fatty acids via β-oxidation and proteins via deamination, and the common endpoint for all three pathways is acetyl coenzyme A (acetyl coA).
b. ATP cannot be transferred around the body, only produced and used within cells, so the body is dependent on efficient transfer of the metabolites and substrates around the body, in order to meet the needs of individual organs under different conditions.
c. Protons (H^+) are passed on to a flavoprotein-cytochrome carrier chain within the cell's cytosol to enable the process by which ATP is regenerated, by giving up an electron.
d. The citric acid cycle is a progressive breakdown of citrate, a 6-carbon molecule, into oxaloacetate, a 4-carbon molecule.

Question 2.16

Concerning cellular anabolic processes, which statement is not true?

a. Glucokinase or Hexokinase is reversed by Glucose-6-phosphatase so that G6P is converted to glucose.
b. Pyruvate Carboxylase reverses Pyruvate Kinase and requires thiamine as a coenzyme.
c. Linoleic, Linolenic and Arachidonic acid are essential polyunsaturated fats and are precursors of prostaglandins.
d. Triglycerides are formed when one glycerol molecule combines with 3 free fatty acids.

Metabolic response to starvation

Question 2.17

A period of starvation combined with the surgical stress response will predispose a patient to insulin resistance (IR). Which of the following is true with regards to IR?

a. The presence of IR in the peri-operative period indicates that a patient has a mild form of diabetes mellitus.
b. As other endocrine markers of the stress response (such as plasma cortisol levels) normalise, IR can be expected to be resolving.
c. Pre-operative administration of carbohydrates will limit the development of IR.
d. IR indicates a shift in the body's metabolic status from a catabolic to and anabolic state.

Question 2.18

The metabolic response to starvation may result in elevated serum glucose through multiple endocrine mediated processes. Which of the following does **NOT** contribute to serum glucose elevation after short-term (pre-operative) starvation in an otherwise well patient?

a. Gluconeogenesis
b. Ketogenesis
c. Lipolysis
d. Glycogenolysis

Question 2.19

The metabolic response to stress involves a neuroendocrine and an inflammatory/immune component. When a stressor (e.g. pain) is detected and signalled to the central nervous system a response will be triggered resulting in the activation of the sympathetic nervous system and hypo-thalamic pituitary axis. Which of the following statements is true with regard to the neuroendocrine response?

a. The SNS response is a slow, sustained response that builds over time.
b. The activation of the hypothalamus–pituitary axis results in the release of ACTH, TSH, GH, FSH and LH by the anterior pituitary gland. But only cortisol levels rise significantly.
c. T3 and T4 levels increase as part of the metabolic response to stress.
d. The neuroendocrine response to stress is triggered by a nucleus in the occipital cortex.

Question 2.20

Failure to appreciate the impact of the metabolic response to starvation and to mitigate it by specific peri-operative measures including pre-operative administration of carbohydrate rich solutions may result in:

a. Reduced post-operative muscle function
b. Increased analgesic requirements
c. Hypothermia
d. Glycolysis

Question 2.21

Which of the following will reduce the likelihood of developing insulin resistance in the post-operative period:

a. Peri-operative steroid administration
b. Administration of water in the pre-operative period to prevent dehydration
c. Opiate analgesia to dampen the stress response
d. Early post-operative feeding

Maternal physiological changes in pregnancy

Question 2.22

The physiological effects of pregnancy include:

a. Increased functional residual capacity.
b. A shift in the oxygen-dissociation curve to the right.
c. Anaemia due to a fall in red cell mass.
d. Increased plasma fibrinogen concentration.

Question 2.23

The transfer of drugs across the placenta to the fetus is increased by:

a. An increased maternal/fetal concentration gradient.
b. Increased ionisation of the drug at the pH of the maternal arterial blood.
c. Decreased fetal cardiac output.
d. Fetal metabolic acidosis.

Question 2.24

The following respiratory changes occur in pregnancy:

a. Functional residual capacity reduced by 45% at term.
b. FEV_1 and FVC reduce moderately at term, the ratio remains unaltered.
c. Residual volume decreased by 15%
d. Expiratory reserve volume increased by 25%

Question 2.25

During pregnancy:

a. Total peripheral vascular resistance decreases.
b. Plasma cholinesterase concentration increases.
c. Blood glucose concentration increases.
d. Pulmonary vascular resistance increases nominally.

Question 2.26

Glucose metabolism in pregnancy:

a. is characterised by increased insulin secretion and progressive maternal insulin resistance.
b. is associated with increased fasting and postprandial glucose levels.
c. allows the pregnant mother to preferentially use glucose as fuel for herself and her fetus.
d. is altered by maternal levels of follicle stimulating hormone (FSH) and luteinising hormone (LH).

Physiology of ADH: DI, SIADH & cerebral salt wasting syndrome

Question 2.27

Diabetes insipidus (DI) is one of the causes of altered serum sodium concentrations in hospitalised patient. Which one of the following statements is correct?

a. DI is always a consequence of a failure to secrete ADH from the posterior pituitary
b. DI is a common cause of hypernatraemia in critically ill patients
c. DI can be life-threatening in unconscious patients
d. DI is unlikely if an adult patient is passing less than 1000ml urine in 24 hours

Question 2.28

ADH/Vasopressin is a critical hormone produced in the CNS, that is subsequently secreted into the blood stream where it has several actions. Which one of the following statements is correct?

a. Is produced in the hypothalamus, and released from the anterior pituitary
b. Is produced in a 2-stage process, as a prohormone which is cleaved into the hormone ADH/Vasopressin
c. Is released primarily in response to osmoreceptors, with a response range of 5mOsm/L before they activate osmolality preserving ADH/Vasopressin?
d. Its release is inhibited by various factors including ethanol and alpha-adrenergic agonists

Question 2.29

Syndrome of Inappropriate ADH (SIADH), Diabetes Insipidus (DI) and Cerebral Salt Wasting Syndrome (CSWS) are three causes of hospital plasma sodium concentration abnormalities:

a. Hyponatraemia is the commonest electrolyte abnormality in hospitalised patients and can be caused by all three
b. SIADH is the only one of the three where plasma volume is normal or above normal
c. CSWS can have the same renal osmolality and sodium profile as SIADH because the main sodium loss is via the GIT
d. CSWS is most commonly occurs after severe traumatic brain injury (TBI)

Question 2.30

ADH/Vasopressin:

a. Has non-renal effects that are predominantly mediated through the V2 receptors

b. When first used therapeutically in humans, ADH/Vasopressin was extracted from posterior pituitary cells of animals, but therapeutic versions of ADH/Vasopressin are all synthetic molecules produced in an industrial process.
c. Sub-fornical organ osmo-receptors, located inside the blood-brain- barrier, are the osmo-receptors mostly closely linked to ADH/Vasopressin's role in maintaining serum osmolality
d. ADH/Vasopressin via V1 receptors can improve coagulation by increasing the activity of factor VIII, Von Willebrand Factor and platelet aggregation

Question 2.31

The important osmolality protecting role of ADH/Vasopressin is highly dependent on the ADH receptors in the collecting ducts and distal tubules in the nephrons of the kidney.

a. The dominant water retaining site of action is the Aquaporin-2 water channel on the luminal side of the collecting duct cells
b. The important Aquaporin-2 water channel for preventing excessively dilute urine is on the capillary, not the luminal side, of the cells in the renal collecting system
c. The renal receptor for ADH/Vasopressin is part of a family of at least 3 V receptors which are all transmembrane, ion-channel receptors
d. ADH/Vasopressin has an elimination half-life of 4-5 hours to sustain its osmo-protecting effects

Perioperative temperature management

Question 2.32

An 8-month old infant is booked for a complex posterior sagittal anorectoplasty for repair of an anorectal malformation. During this long operation, after approximately 3 hours you notice her temperature has dropped to 35.3^{o}C. What is the best way to treat the hypothermia?

a. Set the room temperature at 29 degrees Celsius
b. Warm IV fluids
c. Forced air warmer
d. Humidified inhaled air

Question 2.33

An 8-month old infant is booked for a complex posterior sagittal anorectoplasty for repair of an anorectal malformation. During this long operation, after approximately 3 hours you notice her temperature has dropped to 35.3^{o}C. The primary cause of heat loss at this stage is:

a. Radiation
b. Convection
c. Conduction
d. Evaporation

Question 2.34

When considering perioperative hypothermia

a. The pattern of intra-operative hypothermia has 2 phases
b. Induction of general anaesthesia leads to a core temperature drop of < 0.5^{o}C within the first hour
c. The extent of redistribution hypothermia is primarily related to the initial difference between core and peripheral temperatures
d. Conduction contributes most to heat loss during the linear phase of hypothermia

Question 2.35

An 8-month old infant is booked for a complex posterior sagittal anorectoplasty for repair of an anorectal malformation. During this long operation, the most reliable monitor of core temperature would be a temperature probe:

a. in the rectum
b. on the forehead
c. in the nasopharynx
d. in the oesophagus at the level of the cricoid

Question 2.36

Regarding heat production in the neonate:

a. Brain metabolism does not significantly contribute to resting heat production
b. Only mild to moderate hypothermia will induce shivering
c. Non-shivering thermogenesis is triggered via parasympathetic innervation
d. Metabolism of brown fat can double the neonate's baseline heat production

DIC & Physiology of coagulation

Question 2.37

You are providing an anaesthetic for a healthy young woman undergoing a caesarean section. After delivery of the baby she becomes hypotensive, obtunded and develops severe hamorrhage. You suspect amniotic fluid embolism. Which statement best describes the coagulation cascade after platelet activation?

a. Kallikrein activates factor XII with a cascade ultimately leading to the production of factor Xa causing fibrinogen to be converted to fibrin
b. Tissue factor activates factor VII, a cascade leads to fibrin formation causing prothrombin to be converted to thrombin
c. Tissue factor activates factor VII, a cascade leads to thrombin formation causing fibrinogen to be converted to fibrin
d. Tissue factor activates factor VIII with a cascade ultimately leading to the production of factor Xa causing prothrombin to be converted to thrombin

Question 2.38

A 60 year old male is being cared for in the intensive care unit for sepsis following perforation of the colon. He develops petechiae and excessive bleeding is noted after central line insertion. DIC is diagnosed. What is the initial event in this process?

a. Activation of the coagulation cascade by bacterial components and damaged host cells
b. Pathological activation of the anticoagulant system, particularly protein S and Tissue Factor Plasminogen Inhibitor
c. Low platelet count due to bone marrow suppression in sepsis
d. Prekallikrein causing complement activation and neutrophil chemotaxis

Question 2.39

You are caring for a patient admitted with a diagnosis of pulmonary embolism. The patient is on an intravenous heparin infusion. They develop a ventilator associated pneumonia. The platelet count is 30. The PI is normal, the PTT is prolonged and the fibrinogen levels are normal. What is the most likely diagnosis?

a. Disseminated intravascular coagulation

b. Thrombotic thrombocytopaenic purpura
c. Heparin induced thrombocytopaenia
d. Idiopathic thrombocytopaenic purpura

Question 2.40

A 25 year old male was injured in a motor vehicle accident. He undergoes a laparotomy for hepatic injury and the surgeon notes that bleeding is difficult to control and suspects trauma-induced coagulopathy. What is the mechanism of this phenomenon?

a. Anticoagulant factors released by traumatised tissue and fibrinolysis
b. Circulating procoagulant factors, fibrinolysis and consumption coagulopathy
c. Hypothermia causing platelet dysfunction
d. Metabolic acidosis causing coagulation factor dysfunction

Question 2.41

A 50 year old patient is in the intensive care unit with Gram negative sepsis. The platelet count is low, PTT and PT are prolonged and fibrinogen levels are low. Which treatments will you administer during treatment of a gastrointestinal haemorrhage?

a. Whole blood and cryoprecipitate
b. Packed red cells, tranexamic acid and fresh frozen plasma
c. Recombinant factor VII, packed red cells and fresh frozen plasma
d. Packed red cells, platelets, fresh frozen plasma and cryprecipitate

Splanchnic physiology

Question 2.42

The splanchnic system receives nearly 25% of the cardiac output through three large arteries: the celiac artery and the superior and inferior mesenteric arteries

a. About 25% of the splanchnic arterial flow goes directly to the liver via the hepatic artery; the remaining 75% reaches the liver after perfusing the pre-portal organs.
b. The hepatic arterial flow can be estimated as the difference between splanchnic blood flow and total hepatic venous efflux.
c. The hepatic artery and the arteries of the pre-portal splanchnic organs have mean pressures of approximately 90mmHg. The portal venous pressure is only slightly lower at around 70mmHg.
d. Hepatic arterial and portal venous blood flow interact closely via the “hydrodynamic” interaction (buffer response). This tends to maintain total liver blood flow as a constant with the hepatic artery and portal vein each providing about 50% of the blood flow.

Question 2.43

Resting splanchnic blood flow is typically 30ml/min/100g of tissue (25–30% of the cardiac output). The splanchnic oxygen consumption at rest is approximately 20–35% of whole body oxygen consumption.

a. Blood flow may vary from <10 ml/min/100g in low cardiac output states or to 250ml/min/100g after a meal and can be maintained even during physiological stress.
b. The oxygen extraction ratio can increase to close to 90% in extreme conditions of stress.
c. The gut and the liver are equally susceptible to ischaemia during short episodes of hypoxia.
d. The surface area of the gut mucosa is extensive and created by villi and microvilli. It is the metabolically active area in the gut and receives most of the total resting Splanchnic blood flow.

Question 2.44

Numerous intrinsic and extrinsic factors influence the splanchnic circulation and contribute to

autoregulation.

a. The intrinsic factors include the theories of metabolic control, myogenic control, and local humoral control
b. The extrinsic factors include sympathetic innervation, local vasoactive substances and systemic haemodynamic changes.
c. Local humoral vasodilators include adenosine, nitric oxide and angiotensin II
d. All of the splanchnic vasculature is sympathetically innervated except for the capillaries. Alpha and beta receptors are present throughout.

Question 2.45

In times of hypovolaemic or haemorrhagic stress the sympathetic response mobilises up to two thirds of the splanchnic blood volume reservoir (800mls) into the central circulation to stabilise cardiac output.

a. This mobilisation is due to the alpha-adrenoceptor stimulation expelling blood throughout the splanchnic vasculature producing a rapid increase in venous return.
b. This mobilisation is due to alpha-adrenoceptor stimulation expelling blood from the splanchnic capacitance vessels producing a rapid increase in venous return.
c. This mobilisation can occur regardless of underlying volume status and sympathetic tone.
d. This splanchnic circulation will rapidly return to baseline functioning following resuscitation requiring fluids and catecholamine support.

Question 2.46

Physiological hepatic blood flow is determined primarily by:

1. portal venous flow - determined by the vascular resistance across the intestine
2. hepatic arterial flow - determined by hepatic arterial resistance
3. The hydrodynamic interaction or hepatic arterial buffer response regulates the interaction between the hepatic arterial and portal venous flow.

a. Sympathetic nervous activity is the principal neural mechanism that influences hepatic blood flow by increasing the hepatic arterial and portal resistance.
b. Autoregulation plays a more important role in blood flow to the liver than distribution of flow within the liver (microcirculation vs microcirculation).
c. Portal venous resistance is more important than hepatic venous resistance in determining liver blood flow.
d. Sympathetic nerve stimulation reduces the hepatic volume via contraction of the hepatic capacitance vessels via a β_2-drenergic receptors (reservoir effect).

3. PHARMACOLOGY

Insulin & Metformin

Question: 3.1

Continuous Subcutaneous Insulin Infusion (CSII) pumps are encouraged for individuals who cannot obtain target glucose control while on multiple insulin injection regimes and in circumstances in which excellent glycaemic control is desired, such as pregnancy. Which type of commercially available Insulin is best to use with these pumps?

a. Rapid-acting Insulin
b. Short-acting Insulin
c. Intermediate-acting Insulin
d. Long-acting Insulin

Question: 3.2

A male patient known with type 1 Diabetes Mellitus presents in the Accident and Emergency unit with wet gangrene of his left big toe. On further examination, he is found to be in Diabetic ketoacidosis (DKA) with a blood glucose level of 20mmol/l and a potassium level of 3,5 mmol/l. Which insulin preparation is most suitable to administer intravenously to treat this patient?

a. Rapid-acting Insulin
b. Short-acting Insulin
c. Intermediate-acting Insulin
d. Long-acting Insulin

Question: 3.3

Metformin is often prescribed for patients with insulin resistance syndrome. What is the proposed mechanism of action of Metformin?

a. The activation of the PPARγ receptor and regulation of genes involved in glucose metabolism
b. The blocking of K^+ channels and the opening of Ca^{2+} channels in pancreas beta cells
c. The inhibition of intestinal α-glucosidase with a specific action on Sucrase
d. The slowing of glucose absorption from the patient's gastrointestinal tract

Question: 3.4

Mr X is a heavy alcohol user, known with type 2 Diabetes and an estimated GFR of 59 ml/min/1,73m^2. An arterial blood gas reveals a lactate of 3 mmol/l. Which oral antidiabetic agent will you least likely prescribe to him, knowing his medical history?

a. Acarbose
b. Metformin
c. Repaglinide
d. Rosiglitazone

Antimycobacterial/ Antiretroviral and Chemotherapeutic drugs

Question 3.5

The Vinca Alkaloids are a class of chemotherapeutic agents often used in the treatment of lung and breast cancer. With regards to their mechanism of action, pharmacokinetic and pharmacodynamic properties, the most correct statement is:

a. Vinca alkaloids disrupt microtubule function in the mitotic spindle apparatus
b. The most common adverse effect encountered in the use of vinca alkaloids is gastrointestinal upset
c. The predominant route of elimination of vinca alkaloids is renal
d. Metabolism is independent of the CYP450 system and limited significant drug interactions exist

Question 3.6

With time, newer classes of anti-retroviral agents have become available in South African treatment algorithms. With regards to Dolutegravir:

a. It has a terminal half-life of 6 hours, requiring twice daily dosing
b. Excretion is predominantly renal and renal-friendly dosing regimens are required in renal failure
c. In concurrent tuberculosis infection, dosing should be increased as Rifampicin decreases Dolutegravir concentration
d. It is classified as a fusion inhibitor

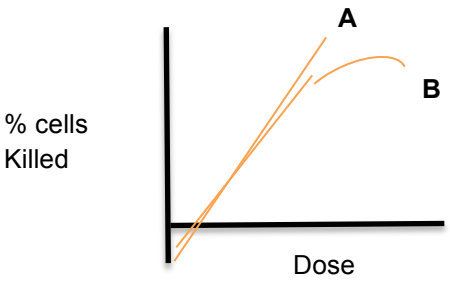
Question 3.7

The mechanism of action of rifampicin includes inhibition of which of the following enzymes?

a. Transpeptidase
b. DNA dependent RNA-polymerase
c. Topoisomerase II
d. RNA dependent DNA-polymerase

Question 3.8

Identify the correct statement regarding two drugs A and B, depicted in the graphic, which have chemotherapeutic effects:



a. A is cell cycle specific
b. B is cell cycle specific
c. Both A and B are cell cycle specific
d. Both A and B are cell cycle non-specific

Question 3.9

A 36 year old woman presents to her local clinic with fatigue, unintentional weight loss and non-specific gastrointestinal symptoms. She was diagnosed with HIV and initiated on antiretroviral therapy 11 months prior to this. She is found to be hyperlactataemic, but has a normal serum pH. With regards to ARV-induced hyperlactataemia:

a. The non-nucleoside reverse transcriptase inhibitors are most often implicated
b. The highest risk occurs with the combination of Didanosine and Stavudine
c. Usually occurs within 3 months of initiation of treatment
d. The offending agent should be stopped immediately, with the remainder of the regimen continued as usual.

Pharmacogenetics

Question 3.10

In acute porphrias

a. All may develop acute neurovisceral crises
b. Protoporhyrinigen oxidase is deficient
c. All gene mutations causing acute porphrias are inherited in an autosomal recessive manner
d. Overall prevalence in European countries is 10 per 100000 population

Question 3.11

The following agent should be considered most unsafe in patients with acute porphrias

a. Hydralazine
b. Etomidate
c. Diclofenac
d. Tilidine

Question 3.12

In a case of malignant hyperthermia

a. the recommended loading dose of dantrolene is 1 mg / kg.
b. the recommended loading dose of dantrolene is 2.5 mg / kg
c. the maximum recommended dose of dantrolene is 10 mg / kg
d. the loading dose of dantrolene should be followed by an infusion of 0.25 mg/kg/hr

Question 3.13

The criteria for stopping dantrolene in a case of malignant hyperthermia are:

a. Return to baseline heart rate, baseline minute ventilation and core body temperature
b. Return to baseline core body temperature and minute ventilation
c. $EtCO_2$ < 6 kPa, with normal minute ventilation and decreasing core body temperature
d. $PaCO_2$ < 6kPa, with normal minute ventilation and decreasing core body temperature

Question 3.14

With regards to succinylcholine which of the following statements is incorrect?

a. Succinylcholine can trigger malignant hyperthermia on its own without a volatile agent
b. The risk of hyperkalaemia with succinylcholine is high with patients with muscular dystrophies
c. The most common plasma cholinesterase variants are the fluoride resistant ones
d. Masseter muscle spasm is usually an isolated adverse event

4. STATISTICS

Introduction to basic statistics

Question 4.1

Hypothesis testing (as determined by the statistical significance of P value) reports:

a. The magnitude of the effect
b. The precision of the estimated magnitude of that effect
c. The clinically importance of an effect
d. The evidence against the null hypothesis

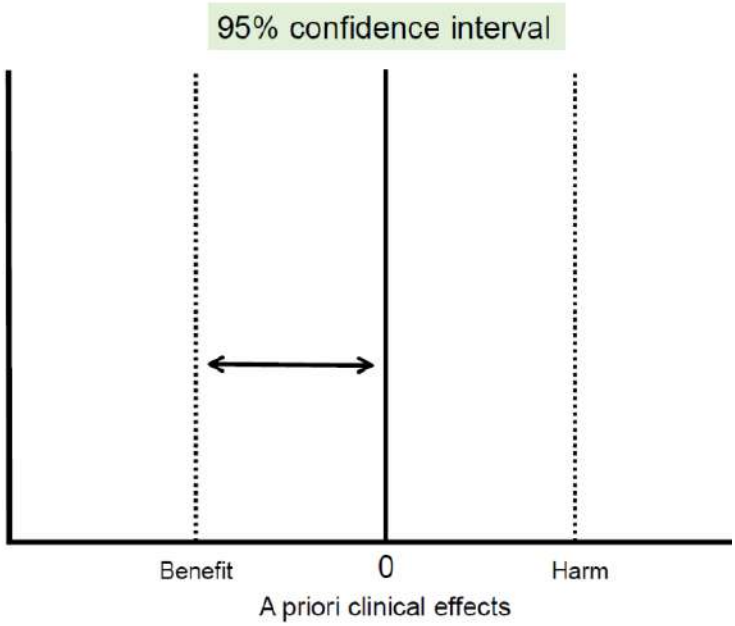
Question 4.2

A P value indicates the strength of evidence against the null hypothesis. A smaller P value

a. Provides stronger evidence that the null hypothesis is false.
b. Decreases the probability of a difference between groups.
c. Signifies statistical significance between groups.
d. Results from a smaller sample size.

Question 4.3

The overlap of the 95% confidence intervals across the line of unity (i.e. no difference), and the lines of benefit (i.e. relative risk reduction) and harm (i.e. increase in risk considered clinically harmful)



The 95% confidence interval shown in the figure is

a. Statistically insignificant and clinically insignificant
b. Statistically significant and clinically insignificant
c. Statistically significant and clinically significant
d. Statistically insignificant and clinically significant

Question 4.4

Randomising participants to study groups balances both known and unknown confounders between the study groups. In randomised controlled trials, it is important to

a. Blind the participants and clinicians
b. To stop the trial early for efficacy
c. Appoint a data and safety monitoring committee
d. Accept deviations to the protocol to keep participants in the trial

Question 4.5

Positive predictive values (PPV), negative predictive values (NPV), sensitivity and specificity and likelihood ratios are used as diagnostic and screening statistics.

a. PPV and NPV is dependent on the prevalence of the disease in the sample.
b. Sensitivity and specificity is dependent on the prevalence of the disease in the sample.
c. Likelihood ratios are dependent on the prevalence of the disease in the sample.
d. Specificity is computed from the group of people with the disease.

Single Best Answer (SBA) Practice Answers

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1. PHYSICS

Humidification

1.1 Answer c

a. False: Energy is required to increase the kinetic energy of water molecules, causing evaporation.
b. False: Energy is not released but is used during the process of humidification.
c. True: The energy required to humidify the air breathed is more than the energy required to heat the air.
d. False: Infants are impacted much more by humidification. They can require up to 20% of their metabolic rate for humidification.

1.2 Answer a

a. True: Using a fresh gas flow of no more than 0.5 L/min. turns a circle system into a good humidifier.
b. False: The dead space of an HMEF will have no bearing but use of an HMEF will improve humidification (especially early on during use of the circle system).
c. False: Excluding the soda lime from the circle system will take away a source of moisture.
d. False: Scavenging happens after excess gas has left the system and will have no bearing on humidification inside the system.

1.3 Answer b

a. False: Mucociliary clearance will decrease.
b. True: Atelectasis will increase as mucociliary clearance decreases.
c. False: Bronchoconstriction may result with decrease in expiratory flow rate.
d. False: The heat energy required to humidify dry gas can only decrease body temperature.

1.4 Answer c

a. False: Absolute humidity is the **mass** of water in a given volume of gas.
b. False: Relative humidity is the amount of water vapour present in a volume of gas as a percentage of the amount of water vapour that is required to fully saturate the same volume of gas **at the same temperature and pressure**.
c. True: Water vapour pressure is the partial pressure exerted by water vapour in a gas mixture.
d. False: Dew point is the **temperature** at which ambient air (at ambient temperature) is fully saturated.

1.5 Answer d

a. False: If the heat from the heated wire did affect the plastic, it would increase the compliance by making the plastic softer.
b. False: Triggering the ventilator will not affect the compliance.
c. False: The hot water humidifier is large and will not affect the resistance in the system.
d. **True: Increasing the compression volume increases the compliance**.

Lasers, fires and explosions

1.6 Answer a

a. True: Coherence, or light in phase is required
b. Collimation or a precisely aligned beam is required
c. High power density is required
d. A narrow spectrum of frequency is required

1.7 Answer c

a. Stoichiometric combustion is the ideal combustion process where fuel is burned completely.
b. Stoichiometric mixture results in the most violent reactions
c. True: Stoichiometric mixture results in no excess reactant being produced
d. There is no excess of the reagent upon completion of the reaction

1.8 Answer d

a. Class I: lasers are safe under all normal uses, even with optical magnification
b. Class 2: Are safe because of the blink reflex, which limits exposure to under one fourth of a second
c. Class 3: Are split into 2 groups on the basis of intensity. Class 3R are within 5x the acceptable emission limit of class 2 in the visible range, class 3B is above that level and is able to cause direct ocular injury
d. True: Class 4 Lasers are high-powered lasers that can cause fire

1.9 Answer c

a. Air contains only 21% oxygen
b. Helium has a higher thermal conductivitity that can delay ignition of a fuel for a few seconds
c. True: Nitrous Oxide (N_2O) is an oxidizer and easily exothermically dissociates, releasing heat and free oxygen
d. Xenon is not flammable because it is inert (chemically inactive)

1.10 Answer a

a. True: Class A fires: if a CO2 extinguisher is used the hot embers could re-ignite when oxygen returns
b. Class B - CO2 extinguisher is used for flammable liquids
c. Class C - CO2 extinguisher is used for electrical equipment as water extinguishers may result in electrocution
d. All of the above

Pulse oximeter

1.11 Answer d

a. Beer's law:
This is a principle employed in pulse oximetry that states the intensity of transmitted light decreases exponentially as the concentration of a substance increase; the path length being constant.

b. Lambert's law:
The principle employed in pulse oximetry that states the intensity of transmitted light decreases exponentially with an increase in distance through a substance; concentration being constant

c. Plethysmography:
Another principle employed by pulse oximetry. It is the measurement of change in volume of an organ or body as volume of blood or air in it changes.

d. Spectrophotometry - True
The principle employed in pulse oximetry of passing radiation through a sample and determining the quantity absorbed.

1.12 Answer b

a. Carboxyhaemoglobin:
The 2 wave pulse oximeter uses red light (660nm) and infrared light (940nm). Carboxyhaemoglobin has a similar absorption spectrum to oxyHb at 660nm and therefore the pulse oximeter cant distinguish between oxyhaemoglobin and carboxyhaemoglobin.

b. Deoxyhaemoglobin - True
Deoxyhaemoglobin and oxyhaemoglobin have different absorption spectra at 660nm and 940nm and therefore they can be quantified by the 2 wave pulse oximeter.

c. Fetal haemoglobin:
Two wave pulse oximetry can't measure fetal haemoglobin. However, the absorbance of red and infrared light is essentially the same as HbA and thus SpO_2 measurement is reliable.

d. Methaemoglobin:
Methaemoglobin has almost the same absorption as deoxyHb at 660nm, but highest absorption of all haemoglobins at 940nm and therefore cant be measured if only 2 wavelengths are used. In order for it to be quantified it needs a co-oximeter with at least 4 wavelengths.

1.13 Answer c

a. Higher absorbance of light at 660nm than 940nm:
The ratio of absorbance of red (660nm) and infrared (940nm) light is calibrated empirically against direct measurements of arterial blood oxygen saturation (SaO_2) in volunteers resulting in the calibration algorithm stored in the pulse oximeter. According to these algorithms a ratio of 1 will give a saturation of 85%, thus a ratio of more than one will give saturations lower than 85%.

b. Isosbestic point:
This is the point at which absorbance for two forms of Hb are identical. Absorbance at any of these points depends only on the Hb concentration.

c. Methaemoglobinaemia - True
Methaemoglobinaemia gives a red/infrared light ratio of 1 and thus saturations of 85%.

d. Red/Infrared light ratio of 0,43:
A red/infrared light ratio of 0,43 according to the calibration algorithm equates to a saturation of 100%.

1.14 Answer b

a. Blue nail polish:
The blue nail polish will give a falsely lower saturation reading via pulse oximetry.

b. Carboxyhaemoglobin - True
Carboxyhaemoglobin has a similar absorption spectrum to oxyHb at 660nm. Absorption of light by carboxyHb at 940nm is very little, but because it has the same absorption as oxyHb at 660nm a patient with significant levels of carboxyHb appear red and thus SpO_2 will be overestimated.

c. Methaemoglobinaemia:

Methaemoglobinaemia has almost the same absorption as deoxyHb at 660nm, but highest absorption of all haemoglobins at 940nm. In a patient with methaemoglobinaemia the pulse oximeter will read 85% regardless of the level of saturation.

d. Methylene blue:
Methylene blue will falsely reduce SpO_2 readings and this can be profound with a median nadir SpO_2 of 65%.

1.15 Answer d

a. Anaemia:
Severe anaemia per se does not cause a falsely low SpO_2, but in someone with true hypoxemia and anaemia SpO_2 can underestimate the SaO_2.

b. Faulty saturation probe:
In this scenario there is a plausible explanation (d) for the lower saturation reading. A faulty probe can be ruled out by checking the saturation of another healthy individual with the same probe to see if it reads normal saturation.

c. Penumbra effect:
This effect refers to an erroneously low SpO_2 reading when the probe is malpositioned on the finger and light traveling to the detector only 'graze' the tissues. In this scenario the probe is tightly secured.

d. Venous pulsations - True
When the light absorbance of venous blood have a pulsatile component it can lead to falsely low SpO_2 readings. Venous pulsations can occur when adhesive fingerprobes are placed too tightly around the finger and in severe tricuspid regurgitation; both which are present in this scenario.

Visco-elastic testing of coagulation

1.16 Answer c

Alpha angle which represents fibrinogen polymerization

1.17 Answer c

CI is the clotting index which is a composite parameter representing the ratio of clot formation versus clot breakdown.

1.18 Answer c

TEG has been shown to reduce the amount of blood products being used during resuscitation

1.19 Answer d

None of the above-mentioned parameters accurately represents platelet function

1.20 Answer b

LY30 is the earliest indicator of fibrinolytic activity and is expressed as a percentage

Nitrous Oxide

1.21 Answer b

Nitrous oxide is a greenhouse gas with global warming potential that is regulated by the Kyoto protocol but not regulated by the Montreal Protocol.

Explanation: Nitrous oxide is a greenhouse gas with global warming potential that is regulated by the Kyoto protocol. The Montreal Protocol however deals with substances that deplete the ozone layer. Nitrous oxide does have ozone depleting potential but as an essential medical gas is unregulated by the Montreal Protocol.

Distractors:

a. Nitrous oxide is a greenhouse gas with global warming potential that is regulated by both the Kyoto protocol and the Montreal protocol.

Explanation: Nitrous oxide is not regulated by the Montreal protocol. It is however regulated by the Kyoto protocol. The Montreal Protocol deals with substances that deplete the ozone layer, not greenhouse gasses.

c. Nitrous oxide is a greenhouse gas with global warming potential that is regulated by the Montreal protocol but not by the Kyoto protocol.

Explanation: Nitrous oxide is regulated by the Kyoto protocol that deals with greenhouse gases. It is not regulated by the Montreal protocol which deals with substances that deplete the ozone layer.

d. Nitrous oxide is a greenhouse gas with global warming potential but as an essential medical gas is unregulated by both the Kyoto and Montreal protocol.

Explanation: Nitrous oxide is both a greenhouse gas and has ozone-depleting potential. As an essential medical gas it is not regulated by the Montreal Protocol which deals with ozone depleting potential. It is however regulated by the Kyoto Protocol which deals with greenhouse gases.

1.22 Answer c

Do not store the cylinder in temperatures below -6 degrees Celsius at 137 bar

Explanation: Entonox has a pseudocritical temperature of -6 degrees Celsius at 137 bar in a cylinder. Under this temperature the gas will separate into its components of oxygen and nitroux oxide, with the oxygen layer on the top. This can result in a hypoxic mixture being delivered to the patient. This process is known as lamination.

Distractors:

a. Do not store the cylinder in temperatures below 36.5 degrees Celsius

Explanation: 36.5 degrees Celsius is the critical temperature of nitrous oxide and not the pseudocritical temperature of Entonox. At temperatures above -6 degrees Celsius Entonox will still be a 50:50 mixture of gas in the cylinder provided the cylinder pressure of 137 bar is maintained. At temperatures below -6 degrees however the Entonox will undergo lamination and separate into it's constituent layers of gas.

b. Do not store the Entonox in a cylinder but use pipeline Entonox at 4 bar

Explanation: Pipeline Entonox has a pressure of 4 bar and therefore it's pseudocritical temperature is -30 degrees Celsius. Storage at this pressure of 4 bar is therefore less likely to laminate and therefore safer for the patient. However the question asks about storage as a gas in a cylinder and does not ask what is safer for the patient.

d. The temperature at which Entonox is stored does not matter as long as the pressure in the cylinder is maintained at 137 bar.

Explanation: Entonox has a pseudocritical temperature of -6 degrees Celsius at 137 bar in a cylinder. Below this temperature the mixture will separate into it's two layers, a process known as lamination. The temperature at which Entonox is stored is therefore important to prevent lamination.

1.23 Answer a

The use of nitrous oxide during general anaesthesia for Caesarean Section is recommended by the NAP5 audit as nitrous oxide has been shown to decrease the risk of awareness.

Distractors:

b. The use of nitrous oxide during general anaesthesia for laparoscopic surgery is recommended by the NAP5 audit as nitrous oxide has been shown to decrease the risk of awareness.

Explanation: The NAP5 audit did not show a decreased risk of awareness with the use of nitrous oxide in general anaesthesia other than during Caesarean Section. Furthermore using nitrous oxide during laparoscopic surgery carries the risk of diffusion of the nitrous oxide into the abdominal cavity due to its higher blood solubility than that of nitrogen. The use of nitrous oxide is therefore contraindicated during laparoscopic surgery.

c. Bispectral index (BIS) monitoring should be used to monitor the level of anaesthesia when nitrous oxide is in use.

Explanation: Nitrous oxide does not suppress the cortical EEG and therefore will not influence the BIS monitor. The use of BIS monitoring in general anaesthesia with nitrous oxide can therefore lead to inappropriately deep levels of anaesthesia.

d. Nitrous oxide inhibits the GABA receptors and therefore has potential in prevention of the development of chronic pain.

Explanation: Nitrous oxide does not inhibit GABA receptors. It does however inhibit NMDA receptors and it is via this mechanism that it is proposed that it shows potential in the prevention of the development of chronic pain.

1.24 Answer c

Nitrous oxide can improve arterial oxygenation due to it's persisting concentrating and second gas effects.

Explanation: Concerns have been raised around potential absorption atelectasis as nitrous oxide is more soluble than nitrogen. Peyton et al however demonstrated that nitrous oxide can improve oxygenation due to its persisting concentrating and second gas effects during anaesthesia.

Distractors:

a. Nitrous oxide can decrease arterial oxygenation due to absorption atelectasis as it is more soluble than nitrogen.

Explanation: Nitrous oxide is more soluble than nitrogen and concerns have been raised for the potential for absorption atelectasis. Studies have however shown that arterial oxygenation actually increases. This is due to nitrous oxide's persistent concentrating and second gas effects.

b. Nitrous oxide will increase the amount of volatile required to achieve MAC (minimum alveolar concentration) due to it's additive effects as a hypnotic agent.

Explanation: Nitrous oxide will **decrease** the amount of volatile required to achieve MAC and not increase it.

d. Nitrous oxide demonstrates increasing anaesthetic efficiency at increasing altitude.

Explanation: Nitrous oxide demonstrates **decreasing** anaesthetic efficiency at increasing altitude. This is due to its decreasing partial pressure as the altitude increases.

1.25 Answer d

The nitrous oxide cylinder is nearing empty.

Explanation: Nitrous oxide cylinders are filled by weight and not by pressure as the critical temperature of nitrous oxide is 36,5 degrees Celsius. This means that the nitrous oxide is compressed and stored as a liquid/vapour at room temperature. The pressure gauge reads the saturated vapour pressure and not the amount of the remaining liquid nitrous oxide. The pressure gauge will therefore only drop as the nitrous oxide cylinder nears empty (the liquid is depleted).

Distractors:

a. The pressure gauge on the cylinder is faulty.

Explanation: Nitrous oxide is stored as a liquid/vapour in cylinders at room temperature. The pressure gauge reads the saturated vapour pressure of the nitrous oxide vapour and not the weight of the liquid nitrous oxide. A sudden drop on the pressure gauge therefore reflects an empty cylinder and not a faulty pressure gauge

b. The cylinder's pressure gauge does not accurately reflect the filling pressure of the cylinder and should therefore be ignored.

Explanation: The pressure gauge does not accurately reflect the filling pressure of the cylinder. Instead the cylinder is filled with liquid nitrous oxide by weight. However the pressure gauge will drop when the remaining nitrous liquid, and therefore vapour, is depleted.

c. The pressure on the nitrous oxide gauge is dropping because latent heat of vaporisation is cooling the cylinder, thereby dropping the saturated vapour pressure of the nitrous oxide.

Explanation: When a nitrous oxide cylinder is opened it will indeed drop the cylinder temperature due to latent heat of vaporisation lost. It is however unlikely that this drop in temperature will drop the saturated vapour pressure to zero.

Solubility

1.26 Answer d

Polarity in liquids: Polarity (having a charge) of the solvent and solute is critical. "Like dissolves like" i.e. polar solutes dissolve in polar solution.

Distractors:

a. adding heat to an exothermic reaction
b. common-ion effect
c. molecular size in gases

Explanation:

Adding heat to an exothermic reaction

Exothermic reactions have heat a product. Adding heat will drive the reaction towards the reagents resulting in a decrease in solubility. Endothermic reactions, where heat must be added, will drive the reaction towards the reactants and hence increase solubility.

Common-ion effect

Describes the *decrease* in solubility of an ionic compound when a salt that contains that ion that already exists in chemical equilibrium is added to the mixture.

Phase of the two substances is important:

Solids have stronger bonds than liquids and are generally poorer solvents.
Gases exhibit poor forces of attraction - size of gaseous molecules is irrelevant, they will dissolve / mix in another gas irrespective of size.

Large liquid molecules however may have strong bonds between them and when suspended in a solvent may not dissolve completely.

Both the common-ion effect and temperature are governed by the Le Chatelier's principle – the system will shift in the direction so as to oppose the stress imposed on it. This will establish a new equilibrium with a direct effect on solubility.

1.27 Answer d

Independent of the pressure of the gas or vapour: This makes it practical to use as pressure does not have to be defined.

Distractors:

a. corrected to standard temperature
b. dependent on Henry's law
c. independent of temperature

Explanation:

Ostwald's solubility coefficient is *independent* of pressure.
Ostwald's coefficient is not corrected to standard temperature, it is measured and expressed at a known temperature e.g. 37^{o}C in the human body i.e. the coefficient has a different value at different temperatures.

Henry's law of partial pressures states that the amount of a given gas dissolved in a given liquid is directly proportional to the partial pressure of the gas in equilibrium with the liquid. Since Ostwald's coefficient is independent of pressure, it does not depend on Henry's law.

Solubility *is very much dependent* on temperature but it depends of the phase of the solvent and solute. Increasing the temperature of a liquid increases the solubility of the solid (e.g. more sugar can be dissolved in warmer water) but this is the opposite for gases; increasing the temperature of the solvent will lead to less gas being dissolved (increased kinetic energy of the gas particles in the liquid liberates more out of solution i.e. less gas dissolved in the liquid).

1.28 Answer a

It can be applied to phases other than gas and liquid

Explanation:

Both the partition coefficient and Ostwald's coefficient are dependent on temperature.
Phases order is important in a partition coefficient ie Blood : Gas is numerically different to Gas : Blood. Oswald's coefficient is fixed as V_g/V_L but the partition coefficient can be applied to two liquids e.g. oil in water.

1.29 Answer c

oil : gas partition coefficient

Explanation:

Experimentally anaesthetic agents that have a high solubility in lipid tend to (in a linear fashion) display a greater clinical effect at comparable partial pressures.

Blood : Gas partition coefficient is generally, inversely related to potency; the higher the blood : gas partition coefficient the lower the potency.

MAC is a clinical representation of the potency of the anaesthetic i.e. it reflects the potency of the anaesthetic but is not the mechanism or physical property of WHY the volatile has the greater potency. MAC depends (is the dependent variable) on solubility and not the other way round.

Ostwald's coefficient (L_v) is a bit complex but essentially reflects the volume of gas absorbed by a volume of liquid

$L_v = \frac{V_g}{V_L}$ at equilibrium

Where:
L_v is Ostwald's coefficient
V_g is the volume of gas absorbed
V_L is the volume of saturated solution (liquid) i.e. the volume of liquid in which the gas is absorbed.
The blood : gas partition coefficient is based on the Ostwald's solubility coefficient. As mentioned previously, these are generally inversely related to potency.

1.30 Answer d

Increases uptake of that anaesthetic agent

Explanation:

Onset of action is dependent on achieving an appropriately high alveolar partial pressure that reflects the partial pressure across capillary and brain. Highly soluble agents will take longer to achieve a high alveolar pressure and thus have a slower onset of action.

From a clinically relevant point, the second gas effect relates to the phenomenon of N_2O being rapidly taken up by pulmonary blood flow because of a very large alveolar N_2O pressure (concentration) gradient. This rapid uptake from the alveoli results in the increase of the partial pressure of all the other alveolar gases including the anaesthetic agent. In effect it is the N_2O rather than the anaesthetic agent (its solubility is relatively irrelevant) that leads to the second gas effect.

Increased solubility DECEASES the F_A/F_i slope i.e. it takes longer for the alveolar partial pressure fraction to approach inspired partial pressure fraction.

Uptake of anaesthetic is dependent on the solubility of the gas – the more soluble the greater the uptake (the slower the induction).

Transducers

1.31 Answer d

a. Decreasing the length of the cannula/tubing would cause the statement to be correct.
b. Decreasing the compliance of the cannula/diaphragm would cause the statement to be correct.
c. The density of the fluid does not affect the natural frequency of the system.
d. True: The length, compliance and diameter of the cannula/tubing are all determinants of natural frequency.

1.32 Answer c

1.33 Answer b

In an overdamped system, the SBP will under-read, the DBP will over-read, and thus the MAP will remain unchanged.

1.34 Answer d

All options are reasonable causes of discrepancies in BP readings between invasive and non-invasive measurements.

1.35 Answer b

The greater the distance between catheter and the aorta, the higher the systolic peak and pressure. The end diastolic pressure would be lower, resulting in a wider pulse pressure, and the pulse would arrive later.

2. PHYSIOLOGY

Insulin

2.1 Answer d

a. Distractor: Insulin stimulates glycogenolysis

Explanation: Insulin reverses the catabolic effects of insulin deficiency by inhibition of glycogenolysis.

b. Distractor: Insulin stimulates gluconeogenesis

Explanation: Insulin reverses the catabolic effects of insulin deficiency by inhibiting the conversion of amino acids to glucose. Remember the definition of gluconeogenesis: a metabolic pathway that results in the generation of glucose from certain non-carbohydrate carbon substrates (e.g. Amino acids).

c. Distractor: Insulin stimulates protein synthesis

Explanation: Increased protein synthesis is an endocrine effect of Insulin on muscle.

d. Insulin stimulates triglyceride synthesis

Explanation: The endocrine effects of Insulin on the liver is two-fold:

- **Anabolic action:**
  - **Insulin promotes glucose storage as glycogen**
  - **Insulin increases triglyceride synthesis and very-low-density-lipoprotein formation**
- **Reversal of catabolic features of insulin deficiency:**
  - **Inhibits glycogenolysis**
  - **Inhibits conversion of fatty acids and amino acids to keto acids**
  - **Inhibits conversion of amino acids to glucose**

Vitamin D

2.2 Answer b

a. Vitamin D is not water soluble but fat soluble and dermal synthesis provides major source
b. True
c. Vitamin D is not water soluble but fat soluble
d. Vitamin D is not abundantly present in food (fatty fish livers are the exception) and dermal synthesis provides major source

2.3 Answer c

a. Not 3 carbon glycerol backbone - four-ringed cholesterol backbone. 1,25- dihydroxyvitamin D is not the major circulating 25-hydroxyvitamin D (25[OH]D) is major circulating form. 1,25-dihydroxyvitamin D is the most active form.
b. 25-hydroxyvitamin D (25[OH]D) is major circulating form. 1,25- dihydroxyvitamin D is the most active form.
c. True

d. Not a 3 carbon glycerol backbone - four-ringed cholesterol backbone. Hepatic enzyme 25–hydroxylase places a hydroxyl group in the 25 position of the vitamin D molecule, resulting in the formation of 25-hydroxyvitamin D (25[OH]D) The major circulating form is 25[OH]D

2.4 Answer a

a. True
b. D3 undergoes enzymatic conversion in the liver via 25-hydroxylase
c. D3 undergoes enzymatic conversion in the liver via 25-hydroxylase not 1 alpha hydroxylase (renal tubular enzyme).
d. D3 undergoes enzymatic conversion in the liver not kidney via 25-hydroxylase to 25-hydroxyvitamin D2 (25[OH]D

2.5 Answer d

a. Within renal tubular cells 25[OH]D is further converted via 1-alpha-hydroxylase to produce the most active form 1,25-dihydroxyvitamin D
b. Within the renal tubular cells 25[OH]D is further converted via 1-alpha-hydroxylase to produce the most active form 1,25-dihydroxyvitamin D
c. Within renal tubular cells 25[OH]D converted via 1-alpha-hydroxylase to 1,25-dihydroxyvit D
d. True

2.6 Answer c

a. Not a positive feedback system → negative feedback
b. Increase in PTH increases 1-alpha-hydroxylase not 25-hydroxylase \
c. True
d. Not a positive feedback

Ref: Pazirandeh S.,& Burns, D. (2019). Overview of vitamin D. Motil K (Ed.), *Uptodate.* Retrieved 19 January 2021from https://www.uptodate.com/contents/overview-of-vitamin-d/print?search=vitamin

Physiology of Carbon Dioxide

2.7 Answer a

Carbon dioxide is 20 times more soluble than oxygen and the number of molecules in solution is proportional to the partial pressure at the liquid surface (Henry's Law).

Distractors:

b. 25% of carbon dioxide in all forms (solution, buffered as carbonic acid and protein bound) is carried in plasma.
c. Less carbon dioxide is carried in blood at higher temperatures. The higher kinetic energy of gas molecules at a higher temperature causes more gas molecules to break their bonds with the liquid particles.
d. Carbon dioxide partial pressure of alveolar and end-capillary blood is almost identical due to the high solubility and diffusing capacity of carbon dioxide. Even a large shunt will only cause a small gradient.

2.8 Answer c

The higher concentration of carbon dioxide in venous blood drives the conversion of carbon dioxide into hydrogen and bicarbonate ions inside the red blood cell by the enzyme carbonic anhydrase. The hydrogen ions are buffered by intracellular proteins and phosphates. A build-up of bicarbonate in the cell would increase osmolarity and limit the ability of carbonic anhydrase to combine carbon dioxide with water. The intracellular bicarbonate ions are exchanged for extracellular chloride ions by the Band 3 exchange transporter protein, thus maintaining electrical neutrality of the cell and decreasing the intracellular concentration of bicarbonate.

Distractors:

a. This reaction does occur but is not described by the Hamburger effect.
b. Bicarbonate ions diffuse OUT of the cell in exchange for chloride ions – what is described above is the reverse Hamburger effect.
d. This process occurs and is termed the Haldane effect, not the Hamburger effect.

2.9 Answer b

The carbon dioxide dissociation curve is more linear and has no plateau. Carbon dioxide content of blood continues to rise as partial pressure rises. Increasing ventilation of well-ventilated regions of the lung will thus continue to improve carbon dioxide clearance and increasing minute ventilation can compensate for a large shunt (as opposed to the inability to improve oxygenation with increased ventilation in the presence of a shunt).

Distractors:

a. The carbon dioxide concentration change is much larger (almost 3 times greater) for the same change in partial pressures, as the carbon dioxide curve is much steeper and has no plateau.
c. At equivalent partial pressures, the content of carbon dioxide in blood will be much higher than that of oxygen.
d. Just as high carbon dioxide pressures drive the dissociation of oxygen from haemoglobin, by decreasing blood pH; high oxygen concentrations will decrease the affinity of haemoglobin for carbon dioxide and allow its elimination (in the lungs).

2.10 Answer d

The increased activity at peripheral chemoreceptors in response to a decrease in P_aO_2 is potentiated by increases in P_aCO_2 (at the carotid and aortic bodies) and by a decrease in pH (at the carotid bodies only).

Distractors:

a. Central chemoreceptors are not sensitive to changes in P_aO_2. Oxygen only affects activity at peripheral chemoreceptors.
b. The diffusion of carbon dioxide into the cerebrospinal fluid and the liberation of hydrogen ions which then stimulate chemoreceptors is the principal mechanism (the direct effect of carbon dioxide is less important).
c. The lower buffering capacity of CSF means that a change in CSF pH has a more important effect on the level of ventilation than arterial pH does.

2.11 Answer b

The cerebral circulation is very responsive to changes in P_aCO_2 between 3-10 kPa. With severe hypocapnia or hypercapnia the response on the cerebral circulation is attenuated or abolished. Similarly, when perfusion pressure is below the lower limits of cerebral autoregulation, the response to carbon dioxide is abolished.

Distractors:

a. Brain blood flow is not homogenous, and areas of the brain that receive more blood flow have a steeper flow response to changes in P_aCO_2.
c. Acute hypercapnia with P_aCO_2 above 10 kPa can attenuate or abolish cerebral autoregulation, consequently in this setting cerebral blood flow becomes more dependent on mean arterial blood pressure.
d. CBF is reduced by hypothermia and the CBF / P_aCO_2 relation is also altered, with P_aCO_2 having a reduced effect on CBF.

Intermediary Metabolism

2.12 Answer d

Reduced coenzymes (NAD^+ and FADH) are intermediate energy storage compounds that aid electron (and energy) transfer from metabolic reactions (glycolysis and Krebs cycle) to the electron transport chain.

Distractors:

a. Anabolism = synthesis and catabolism = breakdown. Facts inverted
b. Internal stores can also be broken down from cellular components to liberate building blocks and energy
c. End electron acceptor is oxygen – forms water

2.13 Answer c

A proportion of plasma lactate is produced by both erythrocytes and the heart

THe heart does not produce lactate, but rather reduces it. Lactate is metabolised back to pyruvate (which can potentially enter gluconeogenesis) by the liver (50%), heart, kidneys and skeletal muscle. Cardiac substrate utilization is split between carbohydrate and fat energy sources. Considering it in terms of myocardial oxygen consumption: 60% is used in fatty acid consumption, 20% in glucose and 20% in lactate consumption. The heart uses entirely aerobic energy production pathways but when challenged with ischaemia, lactic acid is not cleared from the myocardial cell into the plasma – it accumulates, the myocardial cell becomes acidotic, cellular processes cease and the cell dies.

Distractors:

a. Hyperlactaemia is variably associated with acidaemia.

   Explanation – Hyperlactaemia is defined as plasma lactate concentration >2 mmol/L. It may arise in a number of circumstances, both physiological and pathophysiological, and it may or may not be associated with an acidaemia depending on concurrent metabolic challenges and an intact buffering system.

b. Ethanol excess produces a Type B lactic acidosis

   Explanation – Lactic acidosis is a metabolic acidosis caused by accumulation of lactic acid in the plasma either caused by tissue hypoxia (Type A) or by failure to clear lactate, without overt tissue hypoxia (Type B). Type A, as caused by tissue hypoxia, may be considered in terms of hypoxaemic, stagnant, anaemic and cytotoxic causes. Type B occurs when there is no evidence of tissue hypoperfusion or oxygenation deficit. It may be subcategorized into B1 (common metabolic derangements): sepsis, renal failure, liver failure, diabetes, malignancy; B2 (toxic causes): metformin, paracetamol, aspirin, ethanol, methanol, ethylene glycol, catecholamines, cyanide, cocaine, etc.; B3 (other causes): tonic-clonic seizures, disorders of carbohydrate metabolism.

d. Lactate is metabolised by the liver, kidneys and skeletal muscle

   Explanation – Producers of lactate are the erythrocytes (as they only generate energy via anaerobic glycolysis and do not possess mitochondria), gut, brain and skeletal muscle, although when lactate concentration exceeds 4 mmol/L skeletal muscle becomes an overall metaboliser of lactate. Lactate is metabolised back to pyruvate (which can potentially enter gluconeogenesis) by the liver (50%), heart, kidneys and skeletal muscle if necessary.

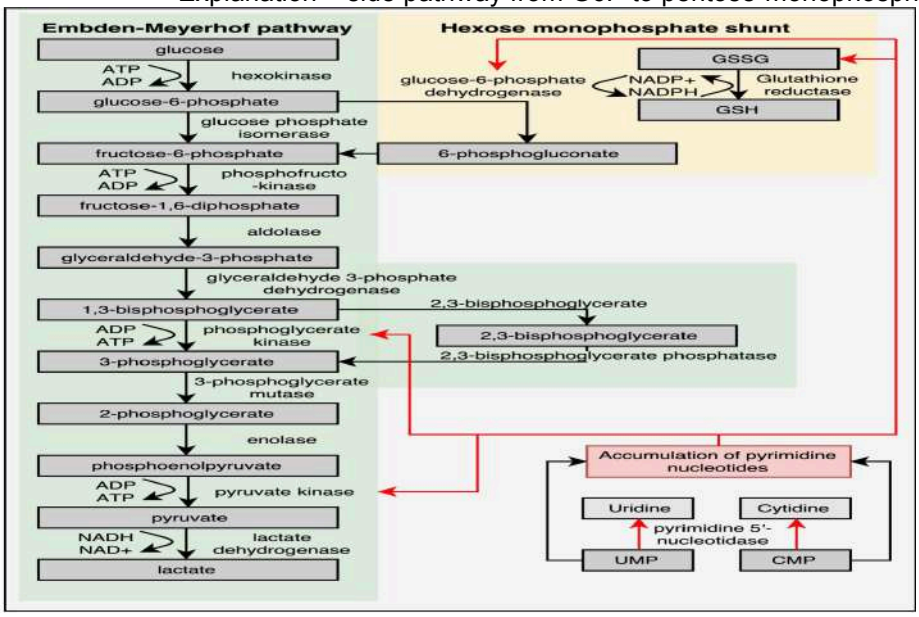
2.14 Answer d

The Leubering-Rappaport pathway leads to the formation of 2,3 Diphosphoglycerate, which is influenced by general metabolism, thyroid and growth hormonal influence, chronic hypoxaemia or anaemia. 1,3-DPG goes to 2,3-DPG through this pathway.

Distractors:

a. Not true, no aerobic. No mitochondria, only anaerobic glycolytic pathway, no Kreb's cycle in RBC.
b. Glycolytic / Embden-Meyerhof pathway, only 2 ATP molecules from each molecule of glucose, via pyruvate and potentially lactate.
c. Glycolysis directly produces reduced forms of pyridine nucleotides for glutathione reduction, methaemoglobin reduction and to neutralise oxidants that may lead to globin degredation.

Explanation – side pathway from G6P to pentose-monophosphate pathway.



2.15 Answer c

Protons (H+) are passed on to a flavoprotein-cytochrome carrier chain within the cell's cytosol to enable the process by which ATP is regenerated, by giving up an electron.

This is false, this process happens inside the mitochondria (Kreb's / citric acid / TCA – tricarboxylic acid cycle), not the cytosol of the cell; where glycolysis occurs.

All other statements are true

2.16 Answer b

Pyruvate Carboxylase reverses Pyruvate Kinase and requires thiamine as a coenzyme.

This is false, as biotin (B7) is required, not thiamine (B1). Thiamine however, is crucial as an indispensable co-factor (TPP: thiamine pyrophosphate) for Pyruvate Dehydrogenase without which the entry into the Kreb's cycle is blocked, which leads to lactate accumulation. TPP is also essential for α-ketoglutarate conversion to succinyl CoA in the Kreb's cycle and Transketolase in the pentose phosphate pathway for regeneration of reduced glutathione from oxidised glutathione and energy production.

Distractors:

a. Glucokinase or Hexokinase is reversed by Glucose-6-phosphatase so that G6P is converted to glucose.

Explanation – Correct statement. Hexokinase is found in most tissues, glucokinase is found in hepatocytes and beta cells of the pancreas. They result in glucose trapping within the cell. Glucokinase has a lower binding affinity and increased capacity as an enzyme compared to hexokinase, so it can more readily respond to changes in cellular needs. Glucokinase is influenced by insulin, whereas hexokinase is not, but does have some negative feedback signalling involving G6P.

b. Linoleic, Linolenic and Arachidonic acid are essential polyunsaturated fats and are precursors of prostaglandins.
Explanation – True statement.

c. Triglycerides are formed when one glycerol molecule combines with 3 free fatty acids.
Explanation – True statement.

Metabolic response to starvation

2.17 Answer c

Administering CHO pre-operatively, either in IV or oral form, will improve insulin sensitivity and increase hepatic glycogen stores.

Distractors:

a. While IR may be considered to be a pre-cursor for metabolic syndrome and type 2 diabetes mellitus the development of IR in the peri-operative period does not indicate that the patient can be expected to go on to develop either of these conditions. The combined stress of pre-operative starvation and the surgical stress response may be sufficient to cause IR in an otherwise metabolically well individual.
b. IR may last for days to weeks, long after the resolution of cortisol, growth hormone and catecholamine levels.
c. Correct
d. IR represents a shift from the anabolic state to the catabolic state with the mobilization of carbohydrates, protein, and fats as fuels to support the process of tissue healing and synthesis of other substances such as acute phase proteins.

2.18 Answer b

With prolonged fasting ketogenesis may occur in the liver as a result of increased gluconeogenesis generating acetyl-CoA. The ketones generated may cause ketonaemia but do not impact serum glucose levels.

Distractors:

a. In the fasting state, glucagon causes the liver to synthesize glucose from oxaloacetate and glycerol (gluconeogenesis).
b. Correct
c. Oxidation of fatty acids derived from adipose tissue lipolysis provides the energy, precursors and effectors for gluconeogenesis thus increasing serum glucose.
d. In the fasting state, glucagon causes the liver to mobilize glucose from glycogen, a process known as glycogenolysis while the enzyme glycogen phosphorylase (under the influence of glucagon) will suppress glycogen synthesis.

2.19 Answer b

Even though the final products of these stimulating factors are not part of the stress response the H-P axis still releases all the stimulating hormones however the peripheral gland response to these pituitary factors is decreased, with the notable exception of cortisol. Peripheral inactivation of the active hormones is the likely mechanism, while alterations in the breakdown of cortisol could account for its increased concentration.

Distractors:

a. the sympathetic nervous system is involved in the fast control of most of the body's internal organs, via the activation of adrenergic receptors. The adrenal medulla is a functional sympathetic ganglion releasing norepinephrine and epinephrine into the bloodstream upon stimulation by the preganglionic neurone. This is the first component of the stress response.
b. Correct
c. Thyroid hormone levels decline during the stress response.
d. The neuroendocrine response is triggered by the paraventricular nucleus and the locus coeruleus in the hypothalamus.

2.20 Answer a

Insulin resistance as a result of the metabolic response to starvation and surgical stress will cause proteolysis with the breakdown of muscle mass to fuel gluconeogenesis. This has been shown to reduce post-operative muscle function contributing to complications and delaying discharge after surgery. The feeding protocols within the ERAS guidelines are designed to mitigate against this development so enhancing recovery.

Distractors:

a. correct
b. While it is important to manage analgesic requirements to reduce the stress response to surgery the metabolic response to starvation will not have a direct effect on analgesic requirements.
c. Hypothermia will contribute metabolic stress as the body seeks to regulate its core temperature by raising metabolism however this is independent of the effects of starvation.
d. Glycolysis will be down regulated by glucagon in the face of starvation as the liver seeks to increase glucose levels.

2.21 Answer d

Early feeding will (especially when combined with efforts to limit starvation pre-operatively) prevent deterioration into a state of starvation and catabolism associated with insulin resistance

Distractors:

a. Exogenous steroid administration will not reduce the metabolic response to starvation and coupled with the surgical stress response may result in dangerously high levels of serum cortisol contributing to peri-operative complications.
b. It is the administration of carbohydrate containing fluids that is important in reducing the response to starvation. Water alone will not prevent it.
c. Good analgesia will reduce the surgical stress response which contributes to insulin resistance. In ERAS protocols multimodal analgesia and regional analgesia such as epidurals are favoured over opiates as they enhance the ability to mobilise and start early feeding.
d. correct

Maternal physiological changes in pregnancy

2.22 Answer d

d. TRUE - Increased plasma fibrinogen concentration.

Hypercoaguable state where fibrinogen levels rise by up to 50% and fibrinolytic activity is decreased. Concentrations of endogenous anticoagulants like antithrombin and protein S decrease.

Distractors:

a. FALSE - Increased functional residual capacity.
Reduced functional residual capacity (with increased closing capacity that may exceed FRC). The closing capacity is increased by age, smoking, obesity and being in the supine position. Studies have shown that in the sitting pregnant patient, the closing capacity remains unchanged.
b. FALSE - A shift in the oxygen-dissociation curve to the right.
The curve shifts to the left: increased minute volume by 40%, tidal volume by 15% and respiratory rate. The resulting mild respiratory alkalosis shifts the curve to the left with increased P_{50} facilitates oxygen off-loading across the placenta.
c. FALSE - Anaemia due to a fall in red cell mass.
Increased red cell mass by 20-30% and increased plasma volume by 40-50% at term results in a dilutional anaemia. There is usually no change in the mean corpuscular volume or mean corpuscular haemoglobin concentration.

2.23 Answer a

a. TRUE - An increased maternal/fetal concentration gradient.

Distractors:

b. FALSE - Increased ionisation of the drug at the pH of the maternal arterial blood.

c. FALSE - Decreased fetal cardiac output.
d. FALSE - Fetal metabolic acidosis.

The rate of transfer of drugs across the placenta is dependent on:

- Lipid solubility
- Degree of ionisation (the non-ionised fraction will cross the placental membrane)
- Protein binding (affected by pH and concentration of plasma proteins)
- pH of maternal blood
- Maternal-fetal concentration gradient (Fick's Law)
- Placental blood flow
- Molecular weight of the drug

2.24 Answer c

c. TRUE – Residual volume decreased by 15%
Lung volumes undergo major changes: expiratory reserve volume gradually decreases during the second half of pregnancy (8-40% at term), and because the residual volume decreases by about 7-20%.

Distractors:

a. FALSE - Functional residual capacity reduced by 45 % at term.
Functional residual capacity reduces by 9-25%.
b. FALSE - FEV_1 and FVC reduce moderately at term, the ratio remains unaltered.
Spirometry remains within normal limits throughout pregnancy. FEV_1, FVC and PEFR remain unchanged or slightly increased with an unchanged ratio.
d. FALSE - Expiratory reserve volume increased by 25 %
Expiratory reserve volume decreases during the second half of pregnancy (8-40% at term).

2.25 Answer a

a. TRUE - Total peripheral vascular resistance decreases.

Heart rate and stroke volume increase as cardiac output increases. Smooth muscle relaxation due to down regulation of the α and β receptors, and prostacyclin release; and the low resistance of the vascular bed of the uterine intervillous space leads to a fall in systemic vascular resistance. Aortic compliance increases.

Distractors:

b. FALSE - Plasma cholinesterase concentration increases.
At term, levels of serum pseudocholinesterase and its activity are low. However, the volume of distribution is increased and so 'scoline apnoea' is rare.
c. FALSE - Blood glucose concentration increases.
Glucose metabolism is characterised by decreased fasting glucose levels and increased postprandial levels.
d. FALSE - Pulmonary vascular resistance increases nominally.
Although both blood volume and stroke volume increase in pregnancy, pulmonary capillary wedge pressure and central venous pressure do not increase significantly. Pulmonary vascular resistance, like systemic vascular resistance, decreases significantly. Serum colloid oncotic pressure is reduced by 10-15%, making pregnant women susceptible to pulmonary oedema.

2.26 Answer a

a. TRUE - is characterised by increased insulin secretion and progressive maternal insulin resistance.

Distractors:

b. FALSE - is associated with decreased fasting glucose levels but increased postprandial levels. Fasting glucose levels are decreased due to increased storage of tissue glycogen, increased peripheral glucose use, decreased hepatic glucose production, fetal glucose uptake.
c. FALSE - The insulin resistance and relative hypoglycaemia result in maternal lipolysis allowing the mother to use preferentially use fat for fuel, preserving the available amino acids and glucose for the fetus whilst minimising protein catabolism.
d. FALSE - the diabetogenic state is driven by human placental lactogen, growth hormone, cortisol, progesterone and prolactin which interfere with insulin receptor signalling in the peripheral tissues and result in falling insulin sensitivity. FSH and LH levels are undetectable in pregnancy due to negative feedback from the elevated levels of oestrogen and progesterone.

Physiology of ADH: DI, SIADH & cerebral salt wasting syndrome

2.27 Answer c

In conscious patients, osmo receptors will drive patients to drink, so that part of the diagnosis of DI is polydipsia. In the unconscious, or sedated patient, they cannot keep up with the losses, and in those patients both the dehydration and the hypernatraemia are life-threatening if not treated.

Distractors:

a. ADH/Vasopressin is indeed released from the posterior pituitary, but Diabetes Insipidus (DI) has both central (ADH secretion failure) and renal/nephrogenic (receptor resistance) forms so the statement that it is "always" due to failure to secrete ADH is incorrect.

b. DI is a rare disorder (less than 1:25 000 prevalence), with many hospital clinicians never seeing it, or having very limited experience with it.

d. Patients with DI pass in excess of 2500ml of urine per 24 hours, and part of the diagnosis is the realisation that urine volume is very large in the face of rising serum sodium and osmolality.

2.28 Answer d

ADH secretion is stimulated by factors in addition to osmolality and blood pressure, and positive stimulating factors include angiotensin II, pain, nausea, hypoglycaemia, nicotine and opiates. Release is indeed inhibited by the presence of ethanol, ANP and alpha-agonists. The inhibitory effect of ethanol explains why intoxicated humans have increased urine output, as without ADH retaining water their kidneys excrete more free water.

Distractors:

a. ADH/Vasopressin is produced predominantly in the hypothalamus, but is secreted in the posterior pituitary along with oxytocin. So the statement that it is released from the anterior pituitary is incorrect.

b. ADH/Vasopressin is produced as a preprohormone (prepropressophysin) which is cleaved into a prohormone, which is further cleaved into the active hormone. So it has a 3 stage process.

c. ADH/Vasopressin is released in response to osmoreceptors, but these are very tightly responsive, keeping the plasma osmolality in a tight band, and respond to changes less than 2mOsm/L

2.29 Answer b

SIADH is essentially excess whole body sodium that is accompanied by even more excessive water retention resulting in low sodium, due to excessive water retention. So these patients are often only distinguishable clinically from patients with CSWS by their fluid overloaded state, including intravascular volume.

Distractors:

a. SIADH and CSWS are both associated with hyponatraemia. DI is exclusively associated with a profound hypernatraemia.

c. CSWS does have a clinical and urine picture that is almost indistinguishable from SIADH, but the sodium losses are still renal, so attributing the losses to the GIT is incorrect.

d. CSWS is overwhelmingly found in patients who have suffered a Subarachnoid Haemorrhage (SAH) and it is uncommon or even rare after TBI.

2.30 Answer b

ADH/Vasopressin was initially extracted from actual pituitary glands. Now all the production is synthetic.

Distractors:

a. Renal effects of collecting ducts and distal tubules are mainly via the V2 receptors, V1 receptors mainly occurring on vascular smooth muscle of the blood vessels.

c. The sub-fornical osmo-receptors are indeed the dominant osmo-receptors in the release of ADH/Vasopressin, but they are not inside the blood-brain-barrier as the BBB is absent at key areas to allow for serum osmo-sensing in certain areas, and for the release of neuroendocrine hormones into the systemic circulation in other areas.

d. ADH/Vasopressin via V2 receptors does improve coagulation by increasing factor VIII, Von Willebrand Factor and platelet aggregation. The exact mechanism is not understood, but it is via the V2 receptors that also act on the kidney, and not the V1 receptors.

2.31 Answer a

Aquaporin-2 is the apparent site of action for the water retention action of ADH/Vasopressin

Distractors:

b. It appears that Aquaporin 2 and 3 are on the non-luminal (baso-lateral) side of the renal collecting systems cell, and are responsible for moving the water out of the cell away from the lumen. So the stem was incorrect as it suggested their role was on the luminal side.

c. The V receptors are all G-protein receptors, mainly activating their effects through cAMP, and then protein kinases. So they are not ion-channel receptors.

d. Arginine vasopressin, that is used therapeutically, has an elimination **half-life of 24 minutes**. So the quoted 4-5 hours is not correct. Terlipressin used for oesophageal varices, has a plasma half-life of 50 minutes and an effect half-life of 5 hours.

Perioperative Temperature Management

2.32 Answer c

Forced air warmer. Forced-air warming and other active warming methods transfer heat to the patient and, over time, return core temperatures to normal.

Distractors:

Warm IV Fluids. The impact of this will vary dependent on intraoperative fluid requirements. Administration of large quantity of cold fluids causes significant heat loss. According to the WHO guidelines, keeping the patient warm is more important than warming blood; warming of blood is required in settings of large volume transfusions (adult: >50 ml/kg/h; children: >15 ml/kg/h)

Set the room temperature at 29 degrees Celsius. The efficacy of prewarming children by increasing ambient temperature in the induction room and operating theatre to 26°C for 30–40 min has been found to be safe and effective. The initial redistribution hypothermia is difficult to treat because flow of heat from core to periphery is massive and transfer of peripherally applied heat to the core requires an hour, even in vasodilated patients.

Humidified inhaled air. With use of low flow rates and semi-closed circuits, heat loss by evaporation from respiratory system is minimal. Less than 10% of metabolic heat produced is lost through the respiratory tract. Hence, heating and humidification of anaesthetic gases to maintain core temperature are not very effective.

2.33 Answer a

Radiation accounts for up to 50% to 70% of heat loss under anaesthesia during the linear phase of heat loss

Distractors:

Evaporation usually contributes up to 15% of heat loss during the linear phase and occurs from cleaning fluids, skin, respiratory and wound.

Convection contributes up to 30% of heat loss during the linear phase and is proportional to air velocity

Conduction contributes up to 5% of heat loss during the linear phase and is proportional to the difference in surface temperatures

2.34 Answer c

The extent of redistribution hypothermia is primarily related to the initial difference between core and peripheral temperatures

Distractors:

The pattern of intra-operative hypothermia has 2 phases. It has 3 phases; Redistribution, Linear, and Plateau

Induction of general anaesthesia leads to a core temperature drop of < 0.5°C within the first hour. A quantitative study of systemic heat balance and regional body heat distribution in volunteers indicated that after 1 h of anaesthesia core temperature decreased by 1.6°C, with redistribution contribution 81% to the decrease

Conduction. Radiation accounts for up to 50% to 70% of heat loss under anaesthesia during the linear phase of heat loss

2.35 Answer c

Nasopharynx. **Core temperature measurement site.**

Distractors:

Rectum. Rectal temperature often seriously lags true core temperature, and it would also be possible given the patients pathology

Forehead. Skin temperatures are approximately 2°C less than core temperature, but the difference between forehead skin and core temperature varies among individuals and within individuals over time

Oesophagus at the level of the cricoid – the tip of the probe should be placed in the distal third of the oesophagus for core temperature measurement

2.36 Answer d

Metabolism of brown fat can double the neonate's baseline heat production. Non-shivering thermogenesis describes the production of thermal energy from the metabolism of brown fat. This is a specialized fat store of the neonate distributed predominantly within the thorax and abdomen, deep to the white fat of the neck and upper thorax. It is characterized by abundant blood supply, sympathetic innervation, and mitochondria. ATP synthesis is uncoupled from respiration within the mitochondria, releasing thermal energy, which can double the neonate's baseline heat production. The removal of placentally derived inhibitory mediators (prostaglandin E_2 and adenosine), the thyroid hormone and catecholamine surges described earlier, rising oxygen concentrations, and cutaneous cooling upregulate non-shivering thermogenesis.

Distractors:

Brain metabolism does not significantly contribute to resting heat production. The metabolically active tissues in the body produce thermal energy. In the neonate the brain, being proportionally larger and more metabolically active than in adults, contributes between 60% and 80% of resting heat production.

Only mild to moderate hypothermia will induce shivering. Shivering thermogenesis is not typically seen in the neonatal period.

Non-shivering thermogenesis is triggered via parasympathetic innervation. See answer for explanation

DIC & Physiology of coagulation

2.37 Answer c

Correctly describes the physiology

Distractors:

a. This is the classic intrinsic pathway, supersede by modern understanding
b. Thrombin and fibrin are transposed
d. Part of the old intrinsic pathway

2.38 Answer a

Accurately describes pathophysiology

Distractors:

b. Pathophysiology involves activation of coagulation, not anticoagulant system
c. This can occur, but is not the primary pathology in DIC
d. This occurs, but involves the inflammatory response

2.39 Answer c

PTT prolonged due to heparin, low platelets in keeping with pathology

Distractors

a. In disseminated intravascular coagulation one would expect fibrinogen to be low
b. PTT would not be raised in TTP
d. Only platelets would be low in ITP, other results would be normal

2.40 Answer b

Correctly describes pathophysiology

Distractors

a. Pathology does not involve anticoagulant factors
c. This may contribute to bleeding, but is not the primary pathology
d. This may contribute to bleeding, but is not the primary pathology

2.41 Answer d

Will be useful in correcting anaemia and replacing low factors

Distractors:

a. Unlikely to be useful in replacing platelets
b. Will not help to correct low platelets and fibrinogen
c. Will not correct low platelets, fibrinogen and other clotting factors

Splanchnic physiology

2.42 Answer a

a. **True: About 25% of the splanchnic arterial flow goes directly to the liver via the hepatic artery; the remaining 75% reaches the liver after perfusing the pre-portal organs.**
b. False: The hepatic arterial flow is part of the splanchnic blood flow. The venous efflux via the hepatic veins represents the total hepatosplanchnic blood flow; therefore the hepatic-arterial flow could be estimated as the difference between portal venous flow and total hepatic venous efflux. (total splanchnic blood flow = portal venous flow + hepatic arterial flow)
c. False: The portal venous pressure is 7–10mmHg, only slightly higher than the pressure in the sinusoids.
d. False: HA:PV blood flow ratio 30:70 / oxygenation ratio 50:50

2.43 Answer b

a. False: Sympathetic vasoconstriction plays an important role in the distribution of blood volume throughout periods of both physiological and pathological stresses such as exercise and major haemorrhage. As blood is diverted into the systemic circulation at this time it is directed away from the gut mucosa.
b. True: The oxygen extraction ratio can increase to close to 90% in extreme conditions of stress.
c. False: Experimental studies suggest that the gut may become hypoxic when its oxygen extraction approaches 70 % Conversely data in humans suggest that the liver is well protected against hypoxia in normal subjects, at least when hypoxic exposure is short.
d. False: The surface area of the gut mucosa is extensive and created by villi and microvilli. It is the metabolically active area in the gut and receives 50% of the total resting Splanchnic blood flow.

2.44 Answer a

Numerous intrinsic and extrinsic factors influence the splanchnic circulation and contribute to autoregulation.

a. True: The intrinsic factors include the theories of metabolic control, myogenic control, and local humoral control.
b. False: local vasoactive substances is incorrect. There is release of noradrenaline mediating α-adrenergic vasoconstriction.
c. False: angiotensin II is incorrect.

Vasodilators	Parasympathetic tone, Increases in PCO2 , decreased PO2 and H+ ,acetylcholine, bradykinin, adenosine,gastrin,secretin,cholecystokinin,VIP,GIP,prostaglandins,substance P, leukotrienes, nitric oxide ,dopamine
Vasoconstrictors	Sympathetic tone, Decreases in PCO2 , increased PO2 and H+, vasopressin, angiotensin II, prostaglandins, peptide YY, neuropeptide YY

d. False: Alpha and beta receptors are present throughout.

Distribution and Function of Adrenergic Receptors
α 1 α 2- β2-adrenergic receptors: hepatic artery and pre-portal arterial supply to the splanchnic organs and hepatic veins.
α-adrenergic receptors ONLY: pre-portal (intestinal) capacitance vessels, portal vein and capacitance vessels of the liver (including sinusoids).

2.45 Answer b

In times of hypovolaemic or haemorrhagic stress the sympathetic response mobilises up to two thirds of the splanchnic blood volume reservoir (800mls) into the central circulation to stabilise cardiac output.

a. False: Alpha-adrenoceptor stimulation results in vaso/venoconstriction and beta-adrenoceptor stimulation in vasodilatation. α- stimulation expels blood from splanchnic capacitance vessels, producing a rapid increase in venous return.
b. True: This mobilisation is due to Alpha-adrenoceptor stimulation expelling blood from the splanchnic capacitance vessels producing a rapid increase in venous return.
c. False: The splanchnic circulation is in close interaction with the systemic haemodynamics under normal conditions. In low blood flow situations the response of the splanchnic circulation depends on concurrent haemodynamic factors.
d. False: If resuscitation is implemented timeously i.e. ”golden hour of resuscitation” splanchnic circulation will return rapidly to baseline with fluid resuscitation. However if catecholamines are required to support cardiovascular stability over and above splanchnic autotransfusion, compensatory mechanisms will take longer to return to the normal physiological state.

2.46 Answer a

Physiological hepatic blood flow is determined primarily by:

1. Portal venous flow - determined by the vascular resistance across the intestine (capacitance vessels)
2. Hepatic arterial flow - determined by hepatic arterial resistance
3. The hydrodynamic interaction or hepatic arterial buffer response regulates the interaction between the hepatic arterial and portal venous flow.

a. True: Sympathetic nervous activity is the principal neural mechanism that influences hepatic blood flow by increasing the hepatic arterial and portal resistance.
b. False: Autoregulation plays an important role in distribution of blood flow within the liver (microcirculation vs macrocirculation).
c. False: Large increases in hepatic venous resistance can cause blood to pool within the splanchnic system and can lead to systemic hypovolemia. Portal venous resistance only becomes important in pathological portal hypertension.
d. False: Sympathetic nerve stimulation reduces the hepatic volume via contraction of the hepatic capacitance vessels via α-adrenergic receptors.

3. PHARMACOLOGY

Insulin & Metformin

3.1 Answer a

a. True: Rapid-acting Insulin
Explanation: Rapid-acting Insulin has the lowest variability of subcutaneous absorption (approximately 5%) of all available commercial insulins. This favourable pharmacokinetic property makes it the preferred Insulin to use in a Continuous Subcutaneous Insulin Infusion (CSII) pump.

b. Distractor: Short-acting Insulin
Explanation: Short-acting Insulin has a variability of 25% of subcutaneous absorption, which makes it a less ideal agent to use in a Continuous Subcutaneous Insulin Infusion pump.

c. Distractor: Intermediate-acting Insulin
Explanation: Intermediate-acting Insulin has a variability of 25% - 50% of subcutaneous absorption, which makes it a less ideal agent to use in a Continuous Subcutaneous Insulin Infusion pump.

d. Distractor: Long-acting Insulin
Explanation: Long-acting Insulin also has a variability of 25% - 50% of subcutaneous absorption, which makes it a less ideal agent to use in a Continuous Subcutaneous Insulin Infusion pump.

3.2 Answer b

a. Distractor: Rapid-acting Insulin
Explanation: Short-acting Insulin is the only type of Insulin that should be used for intravenous administration. Some texts, like UpToDate, also mention the usage of rapid-acting insulin analogues intravenously for the acute management of DKA. Still, the authors emphasize that regular Insulin (short-acting) is their first choice because of the lower cost compared to rapid-acting insulin analogues.

b. True: Short-acting Insulin
Explanation: The hexameric nature of regular Insulin (short-acting Insulin) is the only type that should be administered intravenously because the dilution causes the hexameric Insulin (six Insulin molecules bind together) to dissociate into monomers

immediately. Note that a hexamer is the inactive form of Insulin while a monomer is an active form.

c. Distractor: Intermediate-acting Insulin
Explanation: For acute management of DKA, there is no role for long- or intermediate-acting Insulin; however, long-acting (glargine, detemir) or intermediate-acting (NPH) insulin is administered after recovery from ketoacidosis, before discontinuation of IV insulin, to ensure adequate Insulin is available when IV Insulin is discontinued.

d. Distractor: Long-acting Insulin
Explanation: As for Intermediate-acting Insulin.

3.3 Answer d

a. Distractor: The activation of the PPARγ and regulation of genes involved in glucose metabolism
Explanation: This the mechanism of action of Thiazolidinediones

b. Distractor: The blocking of K^+ channels and opening of Ca^{2+} channels in pancreas beta cells
Explanation: This the mechanism of action of Meglitinides

c. Distractor: The inhibition of intestinal α-glucosidase with a specific action on Sucrase
Explanation: This the mechanism of action of α-glucosidase inhibitors

d. True: The slowing of glucose absorption from the patient's gastrointestinal tract
Explanation: A full explanation of the Biguanides' (Metformin) mechanism of action remains elusive. Their blood-glucose-lowering action does not depend on functioning pancreatic B cells. Currently proposed mechanisms of action include:

- **Slowing of glucose absorption from the gastrointestinal tract with increased glucose to lactate conversion by enterocytes**
- **Reduced hepatic and renal gluconeogenesis**
- **Direct stimulation of glycolysis in tissues, with increased glucose removal from blood.**
- **Reduction of plasma glucagon levels.**

3.4 Answer b

a. Distractor: Acarbose
Explanation: Acarbose is an alpha-glucosidase inhibitor and reduces the postprandial digestion and absorption of starch and disaccharides. Acarbose is contraindicated in patients with inflammatory bowel disease or any other intestinal condition that could be worsened by gas and distension. Acarbose is also excreted by the kidneys and should also not be prescribed in patients with renal impairment. Of all the drug options available for Mr X, Metformin still put the patient in most danger with the possibility of lactic acidosis development.

b. True: Metformin
Explanation: One of the proposed mechanisms of action of Metformin is to block gluconeogenesis and, as a consequence, impair the hepatic metabolism of lactic acid. In patients with renal insufficiency, Metformin accumulates and increases the risk of lactic acidosis. Therefore, Metformin are contraindicated in patients with renal disease, alcoholism, hepatic disease, and in conditions predisposing to tissue anoxia (chronic cardiopulmonary dysfunction) because of an increased risk of lactic acidosis.

c. Distractor: Repaglinide
Explanation: Repaglinide is a Meglitinide and an Insulin secretagogue. This drug modulates Pancreatic B-cell Insulin release by the regulation of Potassium efflux through the Potassium channels. Repaglinide should also be used cautiously in patients with renal and hepatic disease. Of all the drug options available for Mr X, Metformin still put the patient in most danger with the possibility of lactic acidosis development.

d. Distractor: Rosiglitazone
Explanation: Rosiglitazone is a Thiazolidinedione and acts by decreasing insulin resistance. Adverse effects of Thiazolidinediones include fluid retention, macular oedema, and dose-related weight gain. Contraindications to its usage are pregnancy and significant liver disease. Of all the drug options given, Rosiglitazone will be the best antidiabetic drug to prescribe

Antimycobacterial/Antiretroviral and Chemotherapeutic drugs

3.5 Answer a

Vinca alkaloids disrupt microtubule function in the mitotic spindle apparatus. The Vinca alkaloids are anti-mitotic agents. They cause direct metaphase arrest by their interaction with tubulin. While they do have other mechanistic actions which do not relate to their microtubule effects, these do not result in the cytotoxicity necessary for the treatment of various cancers.

a. Answer
b. Distractor: While gastrointestinal upset may occur, the most common side effect is neurotoxicity which presents as a peripheral, symmetric varied sensory-motor and autonomic polyneuropathy.
c. Distractor: The vinca alkaloids are eliminated in faeces. They do however cause renal toxicity.
d. Distractor: The CYP3A4 system plays a large role in the metabolism of the vinca alkaloids, especially vincristine. The azole anti-fungal agents (eg. Ketoconazole) significantly decrease the metabolism of the vinca alkaloid chemotherapeutic agents.

3.6 Answer c

Rifampicin is a potent inducer of drug metabolizing enzymes and drug transporters. Co-administration with dolutegravir reduces concentration, which can be overcome by administration of a twice-daily dose.

a. Distractor: Dolutegravir has a terminal half-life of 12 hours. It is administered as a once daily dose.
b. Distractor: Minimal excretion occurs via the renal route and therefore no dosing adjustment is necessary in renal dysfunction. The effects of dialysis on dosing are however not widely studied.
c. Answer
d. Distractor: Dolutegravir belongs to the Integrase Inhibitor class of ARVs together with Raltegravir.

3.7 Answer b

Rifampicin inhibits bacterial DNA-dependent RNA synthesis by inhibiting the above enzyme. It physically blocks elongation and prevents synthesis of host bacterial proteins.

a. Distractor: Transpeptidase is the enzyme that is necessary for the cross-linkage of peptidoglycan is bacterial cell walls. Penicillins inhibit transpeptidase.
b. Answer
c. Distractor: Topoisomerase II is inhibited by chemotherapeutic agents such as Doxorubicin
d. Distractor: RNA-dependent DNA polymerase is an enzyme also known as Reverse Transcriptase. This enzyme is utilized by viruses, such as retroviruses, to generate DNA copies of themselves.

3.8 Answer b

Cell cycle specific agents inhibit either the M- or S- phase of the cell cycle. With cell cycle specific agents as the dose increases, cell killing increases until a plateau is reached. The plateau is reached once all cancerous cell growth has been halted in either the M or S phase and no further viable cells remain to be killed.

3.9 Answer b

The highest risk occurs with the combination of Didanosine and Stavudine
The risk for hyperlactataemia exists with all of the following drugs, from highest to lowest risk: 1. Combination therapy as above, 2. ddI, 3. D4T, 4. Zidovudine, 5. Lamivudine, abacavir and tenofovir when used in combination with higher risk drugs.

a. Distractor: Nucleoside reverse transcriptase inhibitors (NRTIs) are most often implicated, as noted above.
b. Answer
c. Distractor: Usually develops after some time on anti-retroviral therapy, median of 9 months.
d. Distractor: The recommended management is that the entire ARV regimen should be stopped, and once the patient has recovered clinically an entirely different regimen should be instituted.

Pharmacogenetics

3.10 Answer a

Distractors:

b. Variegate Porphria only
c. Autosomal dominance with variable expression
d. 1-2 per 100000 population

Ref: Continuing education in Anaesthesia, Critical Care and Pain. 2012;12(3):128-133

3.11 Answer b

Distractors:

All should potentially be considered unsafe but the literature says to avoid etomidate (like barbiturates) and use the others with extreme caution only. Indeed none of the above were listed on UK 2018 safe list.

Ref: BJA 200;85(1):143-153

3.12 Answer b

b. is recommended by both North American and European guidelines

Distractors:

a. was the older recommendation
c. no maximum dose. Continue with bolus dosing every 10 min until control is achieved
d. recommended by North American but not European guidelines.

Ref: BJA 2020;125(2): 133-140

3.13 Answer d

Distractors:

a. and b do not have an objective measurement of ventilation
c. $EtCO_2$ underestimates $PaCO_2$

3.14 Answer c

Atypical variants are more common than fluoride resistant ones.

Although less common, succinylcholine can trigger MH without a volatile agent.
MMS does not always go on to MH but the possibility of MH should be considered if it does occur.

Ref: Pharmacogenetic Genomics. 2015;25(12):622-630

4. STATISTICS

Introduction to basic statistics

4.1 Answer d

Hypothesis testing (as determined by the statistical significance of P value) reports the evidence against the null hypothesis
Explanation: The P value reports the probability of rejecting the null hypothesis.

Distractors:

a. the magnitude of the effect
Explanation: The magnitude of effect is determined by the proportional difference between groups which is reflected by relative risk, odds ratio or hazard ratio.

b. the precision of the estimated magnitude of that effect
Explanation: the precision of a magnitude of an effect is reported by the confidence interval.

c. the clinically importance of an effect
Explanation: The clinical importance is determined by a magnitude of effect that clinicians would accept a therapeutic intervention in practice.

Overall: The P value is essentially meaningless for clinical significance. To determine clinical significance, one needs to define what constitutes clinically significance i.e. need to define a clinically significant outcome which would change practice e.g. a 20% relative risk reduction in cardiovascular events.

4.2 Answer a

A P value indicates the strength of evidence against the null hypothesis. A smaller P value provides stronger evidence that the null hypothesis is false.
Explanation: The P value indicates the strength of evidence against the null hypothesis, therefore a low P value, such as <0.05 shows that the null hypothesis i.e. no difference between groups is less than 5%.

Distractors:

b. decreases the probability of a difference between groups.
Explanation: A smaller P value increases the probability of a difference between groups.

c. signifies statistical significance between groups.
Explanation: The statistical significance is set by the researchers. By convention it is usually P<0.05 i.e. accepting a false positive of 5%.

d. results from a smaller sample size.
Explanation: A larger sample size results in a smaller P value. Therefore for the same magnitude of effect in two different studies e.g. 20% relative risk reduction, the study with the larger sample size will have a smaller P value, than the study with the smaller sample size.

4.3 Answer b

The 95% confidence interval shown in the figure is statistically significant and clinically insignificant

Explanation: It is statistically significant as it does not cross the line of unity, but clinically insignificant as the lower confidence interval (i.e. closest to the line of unity) does not cross the line of benefit

Distractors:

a. Statistically insignificant and clinically insignificant

c. Statistically significant and clinically significant
Explanation:
Statistical significance requires the 95% confidence interval not to cross the line of unity. The clinical significance (either benefit or harm) requires the lower CI to cross the line of benefit or the line of harm to be considered clinically significant, as in the figure below.

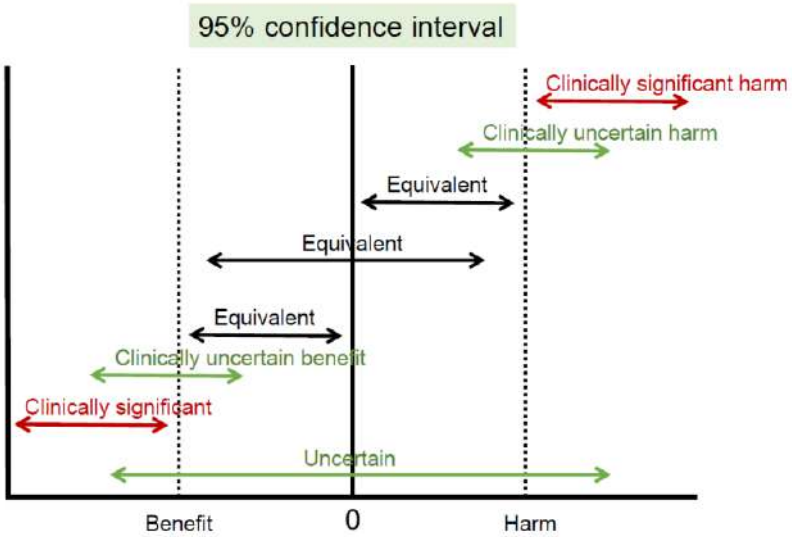


Figure acknowledgement: Prof Jeff Coetzee

d. Statistically insignificant and clinically significant
Explanation: Clinical significance is not possible without statistical significance.

4.4 Answer c

Randomising participants to study groups balances both known and unknown confounders between the study groups. In randomised controlled trials, it is important to appoint a data and safety monitoring committee
Explanation: The committee ensures the safety of participants and to plan, and will have the ability to conduct and act on any interim analyses.

Distractors:

a. blind the participants and clinicians
Explanation: To prevent bias it is important to blind the participants, the drugs administered, the treating clinicians, the outcome assessors and the statisticians.

b. to stop the trial early for efficacy
Explanation: Stopping trials early is associated with positive reporting bias. The decision is taken by the data and safety monitoring committee according to specific trial stopping rules. Although an interim analysis may suggest efficacy, the stopping rules ensure that this is not a false positive finding.

d. accept deviations to the protocol to keep participants in the trial
Explanation: A high level of evidence of the efficacy or effectiveness of a new treatment, requires a rigorous study design to ensure that there is no bias in the management or outcome assessment of participants in the treatment arm.

4.5 Answer a

Positive predictive values (PPV), negative predictive values (NPV), sensitivity and specificity and likelihood ratios are used as diagnostic and screening statistics. PPV and NPV is dependent on the prevalence of the disease in the sample.

Distractors:

b. Sensitivity and specificity is dependent on the prevalence of the disease in the sample. *Explanation: Sensitivity and specificity are not dependent on the prevalence of the disease.*

c. Likelihood ratios are dependent on the prevalence of the disease in the sample.
Explanation: The likelihood ratios are not dependent on the prevalence of the disease

d. Specificity is computed from the group of people with the disease. *Explanation: Specificity is computed from people without the disease.*

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