PART I ANAESTHESIA REFRESHER COURSE

2018

DEPARTMENT OF ANAESTHESIA
AND PERIOPERATIVE MEDICINE
UNIVERSITY OF CAPE TOWN

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Index of lectures

SBA questions and answers prepared by:

Doctors *D Batty, K Bhagwan, B Brennan, M Casey, A de Vaal, A Ernst, M Flint, M Gibbs, R Gray, S Heijke, K Kemp, N Khan, R Llewellyn, T Madden, A Marais, H Meyer, M Miller, F Montoya-Pelaez, A Myburgh, M.Nejthardt, U Plenge, A Reed, C Simons, A Spies, H Steinhaus, K Timmerman, J van Nugteren, A Vorster, G Wilson,* ***and*** Professors *R Dyer, R Hofmeyr, R Parker, J Thomas*.

Principles of Measurement
Arterial blood gas, and electrodes

Dr Dean Nolte
Nelson Mandela Children's Hospital

The measurement of arterial blood gas (ABG) is common in clinical practice, and is essentially in the toolkit of "Point of Care" assessments. Sensors to measure blood gases, electrolytes and metabolites are easy-to-use, automated, and low maintenance: ideal for rapid, reliable, reproducible measurements. As anaesthetists we need to understand:

1. The need for the ABG sampling (what information do we hope to gain from the result. The adage holds true: *"never do a test without knowing what you are going to do with the result"*
2. The basics of electrochemistry (including the definitions anode & cathode, reduction & oxidation)
3. What is going to be measured (and how), and what is calculated (and why / purpose of these values).

This is not only to pass Part I Physics, but ensures that we can request the correct information and helps with future development in this field.
The most important **reasons for blood gas assessment** and analysis include:

1. O_2: diagnostic and therapeutic reasons
2. CO_2: respiratory adequacy
3. Acid-base status
4. Electrolytes (K^+, Na^+, Ca^{2+}) and metabolites (bilirubin, glucose, lactate)

The ABG is thus the cornerstone of measurement of respiratory and metabolic disorders.

Best arterial blood gas measurement:

- Draw blood from an artery, intermittently, using a small needle (22 – 25 gauge) and syringe (heparinised to prevent blood clot formation)
  - (OR from an indwelling catheter)
- Aseptic technique
- Prompt analysis (within several minutes)
  - OR put on ice ASAP and transport to lab (can be delayed by up to 1 hour)
- Put a stopper on the syringe IMMEDIATELY (*prevents arterial blood from interacting with the O2 in air.

Rapid analysis / ice ensures that there is not a rapid decline in the P_aO_2 due to the metabolism that continues to take place by the erythrocytes, white blood cells, etc.

The volume required for measurement by the ABG machine varies from 0.65 – 0.15 ml. The lower the volume, the fewer the number of analytes measured (with decreased likelihood of co-oximetry)

Basics / Definitions of Electrochemistry

1. Electrical potential (V)

Definition: Work per unit charge between two points (i.e. the work expended in moving positive charge). Electrical potential is thus the work done in moving a positive charge from 0 (a reference point) to a point of determination.
It has a positive gradient, which will indicate the magnitude and direction of the driving force (necessitating charge movement).
It is established when one metal is immersed into solution causing metal atoms (from an electrode) to move into the surrounding solution. Thus, the surface of the metal will have a net positive charge, and the solution a net negative charge. This charge is constant dependent on the nature of the immersed metal, the nature and concentration of the solution, and the temperature (if it is maintained).
Two metals within the same solution will establish a predictable potential difference (V) between them.

2. Electric current

This refers to the flow of charge, measured in Ampère's (intensity of flow). This is the S.I. unit of electric current. Current flows from negative to positive; electron flow is from negative to positive. Flow can be in either direction, or both simultaneously.

3. Electro-chemical cell

Two electrodes are found suspended in an electrochemical cell/ solution. Thus each electrode is a single metal conductor within the electrolyte solution. The two sides are separated by a semi-permeable membrane.

The standard electrode

In order to measure electrode potential, we have to be able to start from a reference point. This is the standardized half-cell potential. We make use of a *hydrogen* electrode, which is assumed to have an electrical potential of 0mV.

Hydrogen is at a partial pressure of 1 atmosphere, and is bubbled through a hydrogen-containing solution. The temperature is **25 °C**; $[H^+]$ is **1 mol/l**; pH = **0**.
Platinum is used as the catalyst.

This is essentially very impractical for clinical use. In modern practice: **reference electrode**, with known half-potential (when compared to the "**standard, hydrogen electrode**") is used. The most commonly used reference electrodes in clinical practise are Ag/AgCl, and the $Hg/HgCl_2$ (in a KCl solution). The latter is the calomel electrode.

The usual reference electrode employed is a Ag/AgCl half-cell, in a solution of 4M sodium formate adjusted to a pH of 5.5. a triple membrane protects the electrode.

- Inner: limits diffusion in and out of the electrolyte solution
- Middle: reduces protein interference (blood)
- Outer: protects inner electrolyte solution (4M sodium formate) from rinsing contamination, and from diffusing out.

Convention dictates that the reference electrode is on the LEFT, and the measuring electrode is on the RIGHT.

Electrode types

a) First kind: metal surrounded by the electrolyte solution.
b) Second kind: metal surrounded by its own salt (increases ionic exchange), and then suspended in the electrolyte solution containing the anion of the metal salt.

4. I.S.M.

Membrane potentials result due to selective permeability to anions and cations. The membrane essentially separates the solutions from one another.
Membrane potential** = **Right – Left. If right (measuring) is > Left (reference) then a POSITIVE membrane potential exists. It is VITAL to note that this does represent actual flow of charge, but instead potential difference.

Marked cation activity on the right binds to the membrane → positive charge at the membrane → cation dissociation on the opposite side (left, reference) of the semi-permeable membrane. *The membrane remains "permeable" until equilibrium is reached.*

5. Redox reactions

Two half-cells must work together for flow to occur. The one side is called the cathode, and the other an anode. The basic principles of electrochemistry (which will make your studying lives infinitely easier) can be summarized by the following two acronyms:

O	**I**	**L**	**R**	**I**	**G**
Oxidation	Is	Loss	Reduction	Is	Gain
	(of electrons)				

R	**E**	**D**	**C**	**A**	**T**
	Reduction occurs		at the	**Cat**hode	

6. Compensatory Mechanisms

Some ABG machines require input of F_IO_2 and temperature to accurately perform / calculate results on ABG testing. This allows for temperature compensation.

O_2 / pH / CO_2 are all affected by changes in temperature. Temperature calibration is standardized to a patient with a temperature of 37°C.

- An increase in temperature → change in volume of dissolved gas (in the serum, and within the erythrocytes). This is understood by the application of the *"Ideal Gas Equation"*: $\boldsymbol{PV = nRT}$ (where V is proportional to T).
- Increasing temperatures → increasing vapour pressure (H_2O) → reduced p_aO_2 in the measured blood stream.
- pK_a (dissociation constant) is directly related to temperature; temperature changes the chemical reactions of the buffering solutions (i.e. temperature can ↑ or ↓ rate of change of the reactions)

Blood Gas Parameters, and Measurement

Measured / Determined Physically		**Calculated**
1. pH	2. P_aCO_2	Actual / Standard HCO_3^-
3. P_aO_2	4. Electrolytes	**Base Excess (SBE)**
5. Metabolites (Lactate, Glucose)	6. Haemoglobin, Bilirubin	

The focus of this lecture will be the physical measurement of blood gas values. The calculated values will be dealt with elsewhere in this course.

1. Measurement of pH

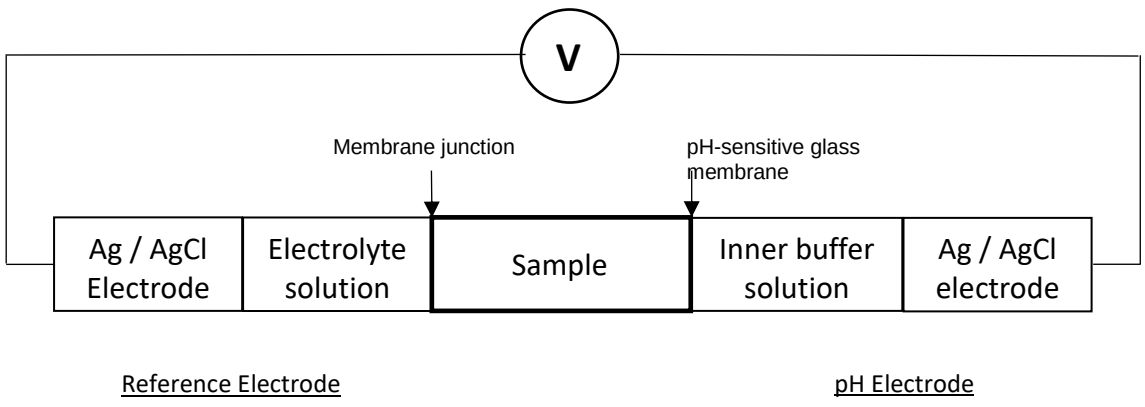
$$\mathbf{pH = -= \log [}\boldsymbol{H^+}\mathbf{]}$$

N.B. *$[H^+]$ and $[H_3O^+]$ are equivocal*

The pH electrode is a "glass" electrode consisting of a 3-dimensional latticework of a central Silicon atom surrounded by 4 Oxygen atoms. There is incorporation of various metal oxides (Ca^{2+}, Na^+) into the glass membrane, allowing for variant sensitivity of the electrode. The metal oxides lose electrons to the incorporated oxygen molecules and thus become **cations**. Charge is displaced across the membrane resulting in the "flow" of current across the glass.

The one side of the glass is exposed to a buffer of KNOWN pH ("reference" electrode); the other side is exposed to blood ("test" solution). The glass membrane is then a partition with differing $[H^+]$ on either side, establishing a potential difference via the concentration gradient. The pH remains constant despite the change in $[H^+]$ due to the action of the inner buffer solution.

The reference electrode will maintain a constant electrical potential despite changes in pH.
The potential difference is measured, and changed to a direct reading of $[H^+]$ which is then converted into a determinable pH value.



Diagrammatic representation of the pH electrode

Reference electrode: completes the circuit, and usually Ag / AgCl (previously Hg / $HgCl_2$)
pH electrode: as described above

These constitute the two half-cells

pH	$[H^+]$ nmol/l
9	1x10
8	10
7	100
7.40 (blood)	40

A decrease in pH of 1 full unit is proportional to a 10x increase in $[H^+]$, and a potential difference generated of 60mV per unit pH.

The pH electrode has a standard life-span of about one year. This is secondary to the consumption of metal oxides (AgCl) in the glass membrane. Calibration is by solutions of known pH: one of pH = 6.841, and the other pH = 7.383 (the latter is the "reference" solution, i.e. point 0mV). There is an air bubble in the solution which allows for expansion and contraction of the buffer solution.

Problems with the pH electrode
The pH electrode measurement requires a constant temperature. Thus in a hypothermic patient there is an increase in the solubility of carbon dioxide in the blood resulting in a **reduction** of p_aCO_2 and thus an **increase** in the pH (falsely). The entire electrode is surrounded by a thermal couple control system to maintain the temperature at 37°C. In addition: electrodes are maintained to be active: ensure that there are no holes in the membranes (this is obviously performed by the machine). Electrodes are also cleaned regularly to remove any debris accumulation.

Salt bridge
- Salt bridges can be places between an electrode and the sample being measured.
- KCl solution is housed within asbestos fibre (or ceramic material). These prevent the contamination of the KCl test solution.
- Need regular replacement.
- Modern day electrodes do not employ the use of salt bridges as they will more likely be surrounded by a triple membrane instead.

Modern day: make direct contact with the solution.

2. P_aCO_2 measurement

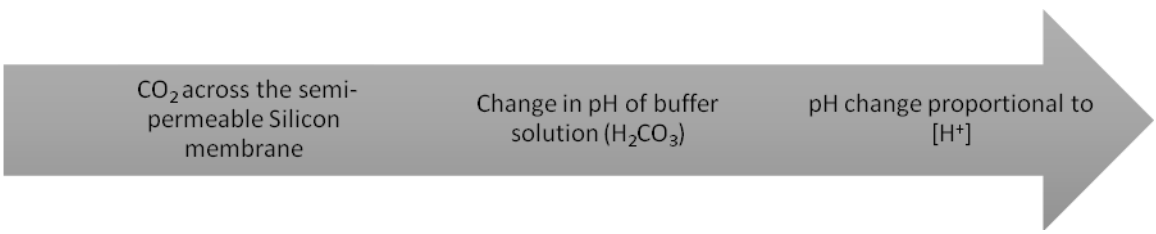
$$\mathrm{pH} = 6.1 + \log_{10}\left(\frac{[\mathrm{HCO_3^-}]}{0.03 \times Pa\mathrm{CO_2}}\right)$$

The Severinghaus Electrode is the mainstay of carbon dioxide measurement from the arterial blood gas. It is essentially a pH electrode, but contains the pH and reference electrodes within **one device.**

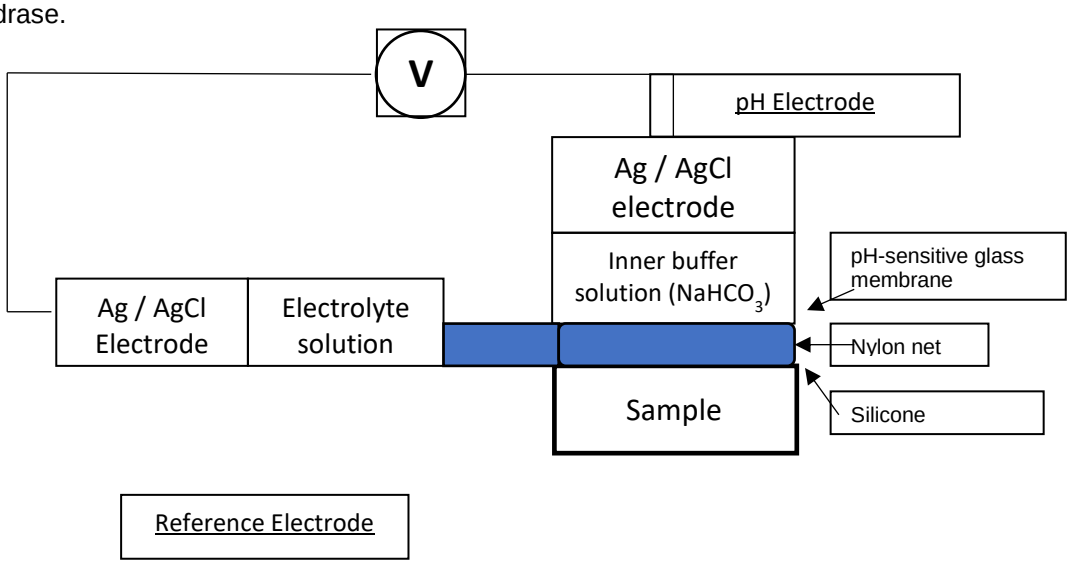
The result takes a long time to determine (1 – 3 minutes) due to the prolonged equilibration, and calibration. (P_aCO_2 α $[H^+]$).

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H_2CO_3^- + [H^+]$$

pH electrode: presented to a thin film of sodium bicarbonate ($NaHCO_3$) via a silicon (OR PTFE OR Teflon) membrane which is permeable to CO_2, but impermeable to blood cells. This equilibrates with the blood (and becomes the "test" solution). There is a buffer solution held in contact with the silicon membrane by nylon or glass wool. The bicarbonate buffer has a concentration of 0.001mol/l.
Calibration: prior to use calibration occurs with two gases of known concentration – 4 and 8 % (in either a gaseous or liquid state).
Reference electrode: houses Ag / AgCl, which is direct contact with the buffer solution.
Silicon membrane: this is permeable to CO_2 (but no other ions that can affect the change of pH).



The change in $[H^+]$ is read by the voltmeter which gives a reading (via calibration) in units of p_aCO_2. The Severinghaus electrode advantageously is accurate and stable. It is, however, slow (due to the diffusion across the plastic membrane, and the time to react with water) and easily prone to electrode damage. It is incredibly temperature sensitive. The reaction is catalysed with the addition of carbonic anhydrase.



Diagrammatic representation of the carbon dioxide electrode

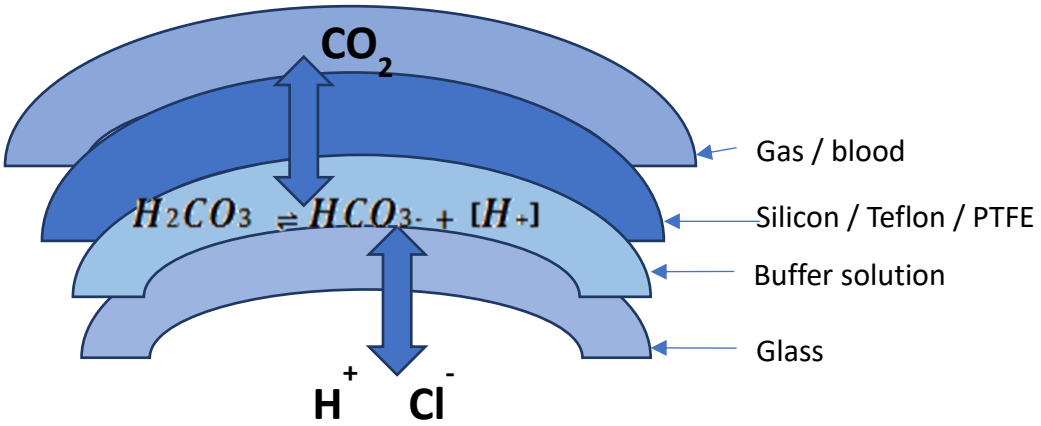
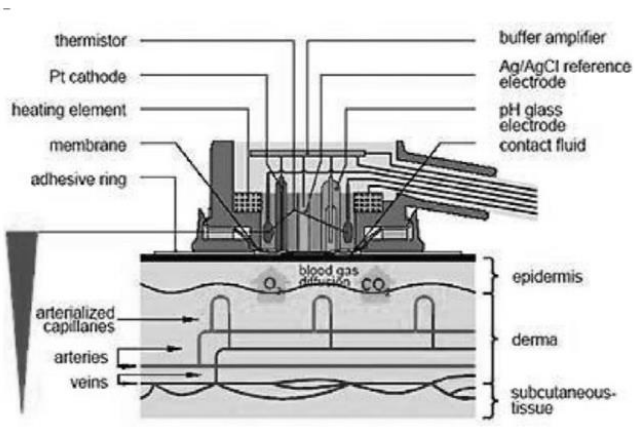


Diagram indicating layers of carbon dioxide electrode

Measurement of arterial paCO2 (and other metabolites) in-vivo

a) Trans-cutaneous electrodes



A transcutaneous gas tension measurement electrode.

This is similar in structure to a full arterial blood gas analyser. BUT the major modifications required include: heating element and a thermistor is added to the electrode. This ensures that the temperature is increased to between 40 – 42°C.

Result: Increased solubility of CO_2
Increased CO_2 production

It is vital to note that the trans-cutaneous (measured) CO_2 is **higher** than capillary CO_2.

One can attain continuous CO_2 measurements as a major advantage. There are, however, problems of

increased risk of skin infections, slow reaction times, and variable correlation between capillary and trans-cutaneous readings (mainly due to the required increased temperature applied).

b) Intra-vascular probes

This is essentially a mini-CO_2 electrode inserted via the arterial line with constant measurement.

c) CO_2 estimation (from $P_{ET}CO_2$)

The normal difference between P_aCO_2 is approximately 0.5 kPa (3.8 mmHg) higher than $P_{ET}CO_2$. In respiratory disease, however, this is totally not applicable (and this means of "estimation" should be limited in clinical practise).

3. P_aO_2 Measurement (and the Clark electrode)

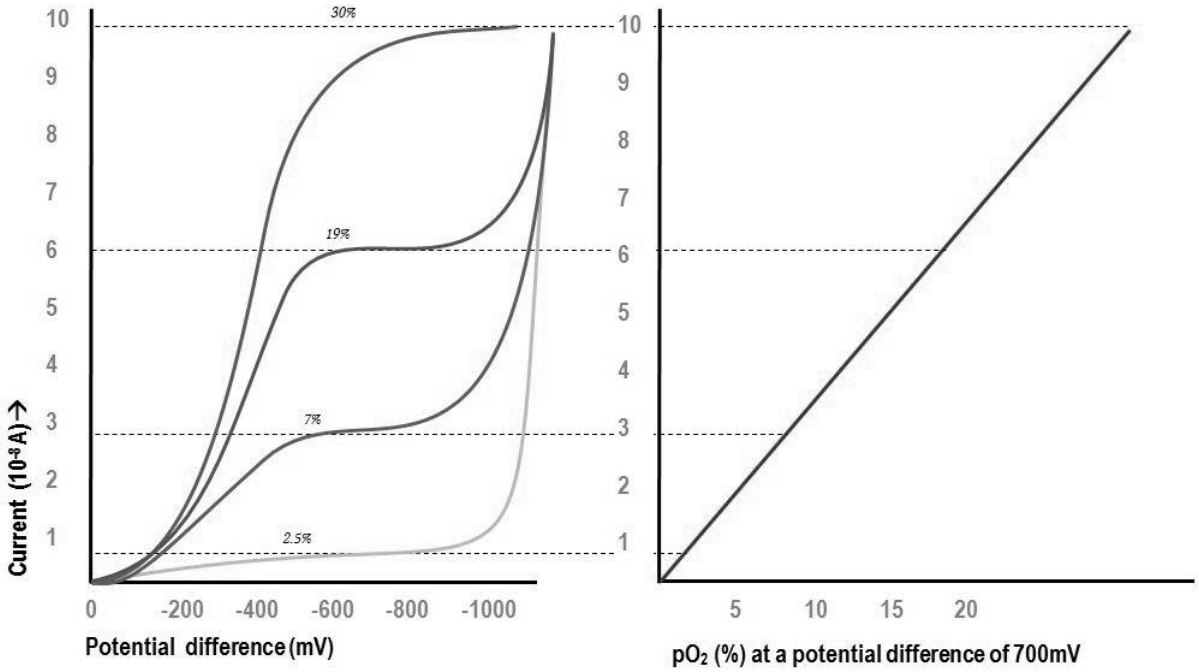
The Clarke electrode measures the tension of oxygen in solution, which is directly proportional / equated to oxygen content of the blood (or gas mixtures: c.f. F_I / F_EO_2). The principle is that a certain number of O_2 molecules within a salt solution will produce a current. *Ohm's Law* is the governing principle:

$$V = IR$$

BUT, R (resistance) is constant, and thus:

$$V \propto I$$

Thus increasing [O_2] results in a higher current produced. By increasing the voltage applied from 0 – 0.45 V the resultant current increases for any P_aO_2. The current reaches a plateau at a potential difference (V) of 0.45 – 0.85 V. We can then observe that there is a failure of the ever-increasing V to drive any further O_2 reduction (at the cathode). Different plateau pressures will be generated/ elucidated dependent on the partial pressures of O_2.



Polarogram

Current is plotted on the y-axis, and voltage on the x-axis. The resultant plot of ***P_aO_2 : plateau*** *of Current is a straight line.*

Polarogram definition: Graph plotting current against potential (i.e. voltage: [anions] in solution); used to determine concentration and nature of ions in solution.

The Clark electrode

The Clark electrode is cheap, reliable and small, requiring no external power supply. There are two electrodes within a single unit, both of which are found behind a **single** semi-permeable membrane. This is a polypropylene membrane (O_2-permeable), preventing bacteria/ proteins/ sediment traversing it. These interfere with the measurement and interpretation of the oxygen values (especially the bacteria which consumes excess O_2 and thus skew values).

The determination of current flow is by the use of the Polarogram (as explained above).

Electrodes:

Platinum cathode	**Ag/AgCl Anode**
➢ The platinum wire cathode acts as a catalyst.	➢ Increases stability of the circuit ➢ Guards against drift due to concentration of the P_aO_2–electrolyte (usually KCl @ 0.1 mmol) ➢ Electron-donor (i.e. Oxidation)

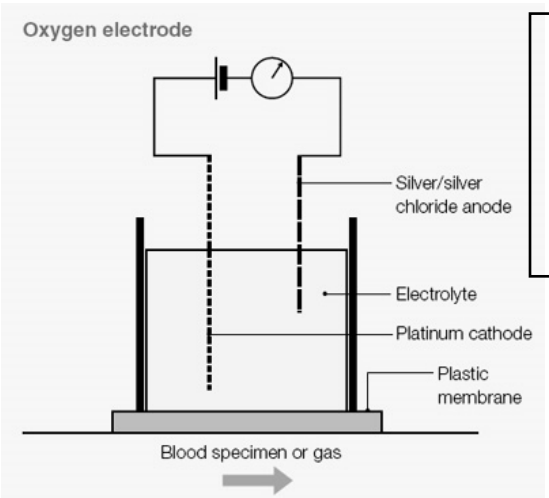
Electrolyte solution: contains phosphate (PO_4^{3-}) buffer, and allows for the O_2 to dissolve

Voltage applied: 0.63V (across the electrodes)

The Platinum cathode measures electrical activity which is equated to oxygen tension (and NOT actual P_aO_2). This is determined by the concentration of the O_2. Increased electron uptake will cause a resultant increase in electrical flow in the circuit (O_2 tension → electricity). The response times are **incredibly slow** (± 10 minutes) due to:

- Polypropylene membrane which O_2 needs to cross (very slow process)
- Oxygen consumption in the immediate vicinity of the membrane.

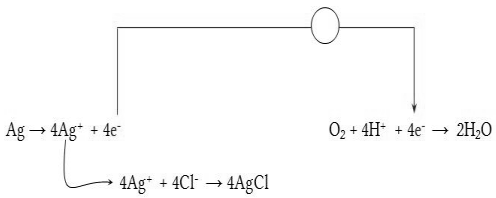
There is a mathematical calculation applied to this (so that we do not have to wait as long).



$4\,Ag \rightleftharpoons 4\,Ag^+ + 4\,e^-$ Oxidation (LOSS) at Ag / AgCl ANODE

$O2 + 4\,H^+ + 4\,e^- \rightleftharpoons 2\,H2O$ **RED**uction at Platinum (Pt) **CAT**hode

The flow of current flows directly proportional to the number of oxygen molecules present (i.e. increased current results in increased flow).

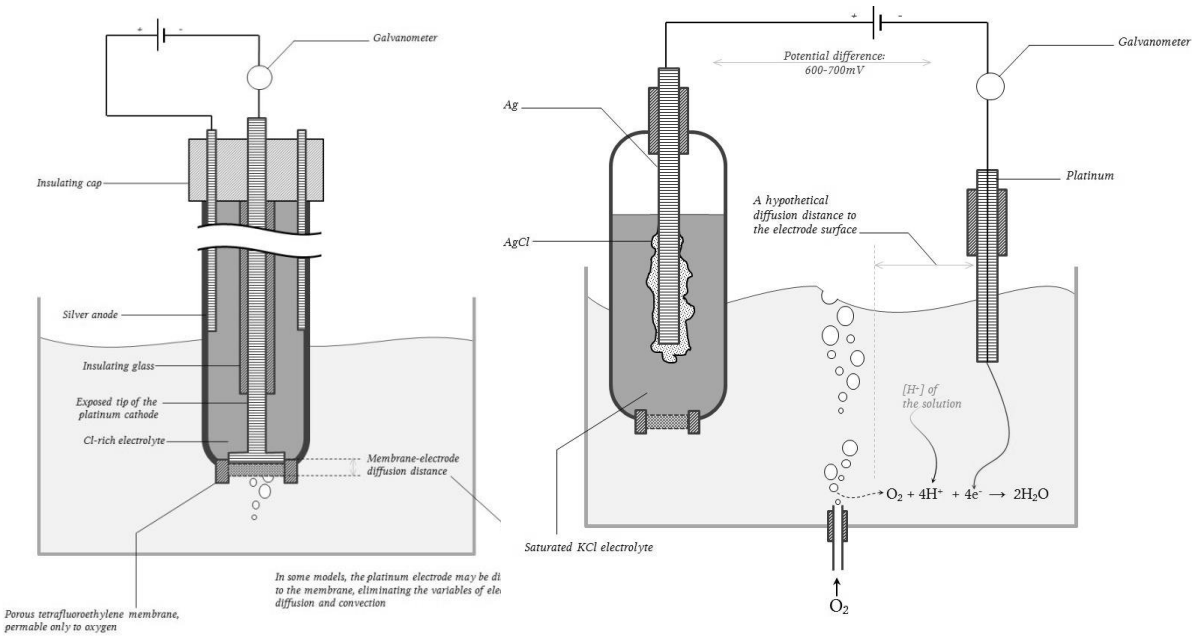


Components of the Clark Electrode

Limitations of Clark electrode:

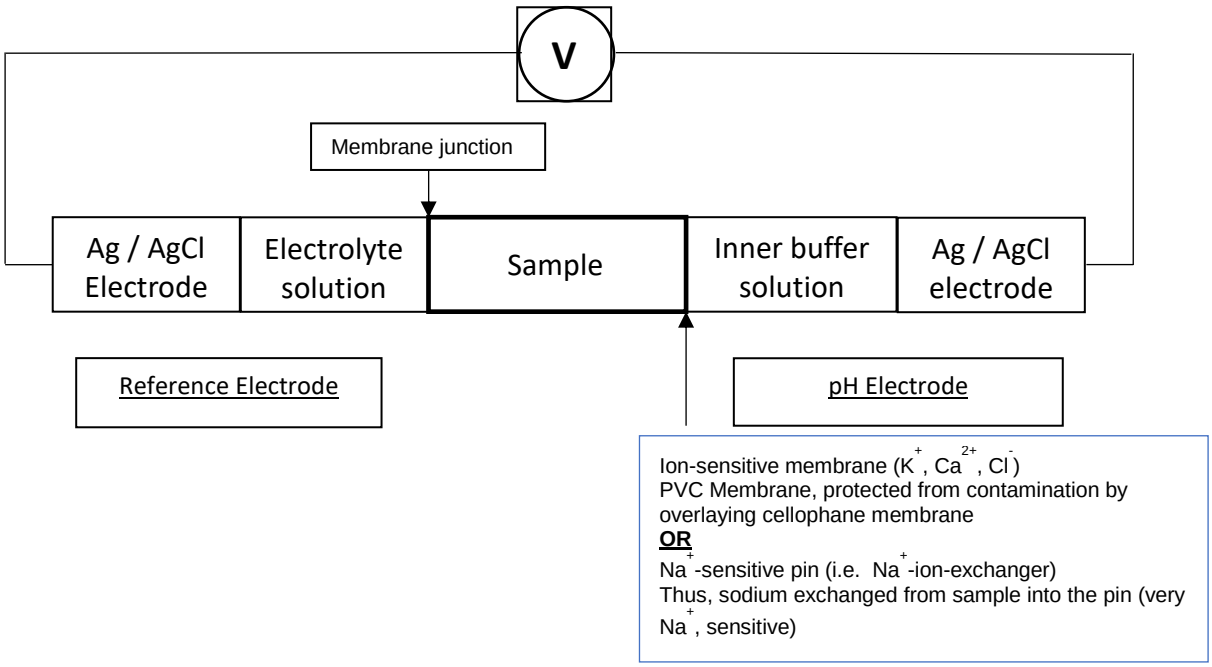
- The electrode is incredibly temperature-sensitive
- Protein deposits from blood samples can eventually block the inflow channel
- The semi-permeable membrane can easily be punctured with needles (from introduced sample), and thus require regular checking
- Halothane (which leads to a falsely-elevated O_2)
- There is a slow response time (actual is 15 – 20 seconds)

The shelf-life of the electrode is limited by exposure to O_2: usually 6 –12 months.



4. Measurement of electrolytes (Na^+, K^+, Ca^{2+}, Cl^-)

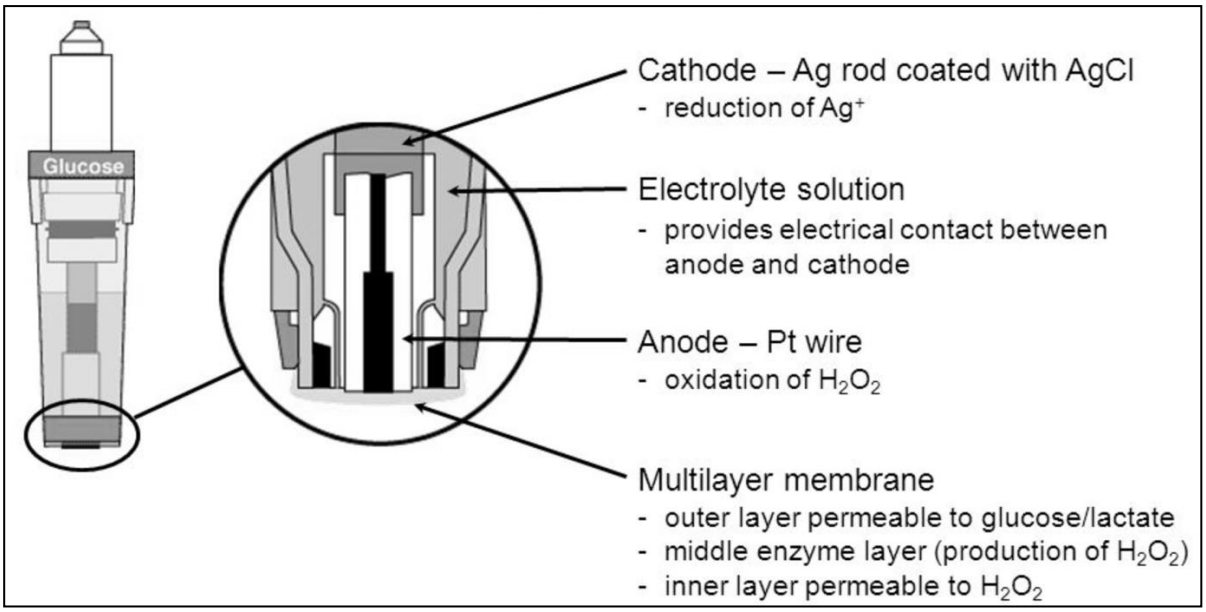
This is done by using the "standard electrode" (discussed in the introductory part of these notes, and refer to the figure below).
Essentially this is made up of a measuring and a reference electrode.
K^+, Ca^{2+}, Cl^- measuring electrode: Ag/AgCl electrode covered with an ion-specific, selective PVC membrane. Cellophane covers this PVC membrane, protecting it from contamination.
Na^+ measuring electrode: Na^+-ion exchanger (Na^+-sensitive pin) replaces the PVC.
Calibration of all systems are performed with standard solutions of known ionic content.



Diagrammatic representation of the electrodes measuring electrolytes

5. Measurement of metabolites (glucose, lactate)

The measurement of glucose and lactate are vital by a rapid, reliable and reproducible means. These values are determined by the oxidation of H_2O_2 (hydrogen peroxide). There are two electrodes in the electrolyte solution. It is important to note that there is a silver/ silver chloride (Ag / AgCl) CATHODE and a Platinum (Pt) ANODE (this contrasts with the Clark electrode). Each electrode is then covered by a 3-layered membrane (see image below for explanation of each of these layers).

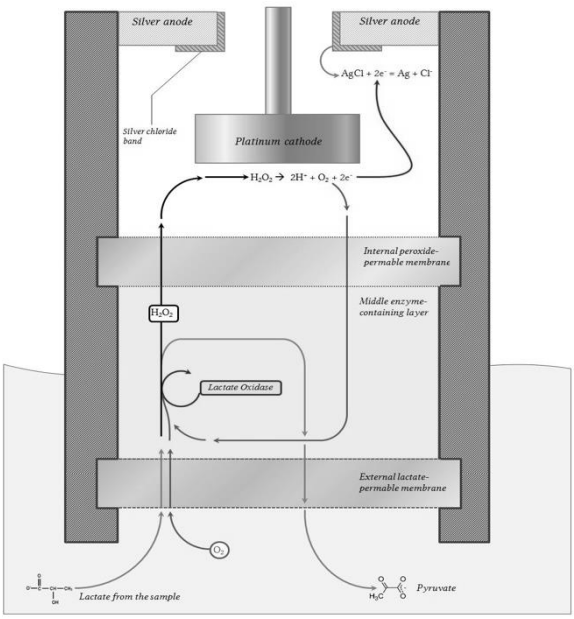


The Standard setup for a metabolite electrode

Ammeter: measures current, determined by the degree of concentration of glucose or lactate. It is thus calibrated to read [glucose] or [lactate].

It is important to note that there is no change in pH of the solution, despite the production of H^+ ions. This is due to buffering occurring in the electrolyte solution.

The significant difference between the lactate and glucose electrode is the presence of the metabolite-specific middle enzyme layer (and the permeable outer layer).



Metabolite electrode (Lactate)

Glucose —*glucose oxidase*→ Gluconic Acid + H_2O_2

Lactate —*lactate oxidase*→ Pyruvate + H_2O_2

The H_2O_2 produced then diffuses (across the inner membrane) to the anode.

$H2O2 \rightleftharpoons 2\,H+ + O2 + 2\,e-$ Oxidation at Platinum ANODE

$2\,Ag+2\,e- + \rightleftharpoons 2\,Ag$ **RED**uction of AgCl into Ag (**CAT**hode)

The flow of current flows directly proportional to the metabolite concentration present (i.e. increased current results in increased flow).

6. Measurement of bilirubin and co-oximetry (i.e. Spectrophotometry)

Spectrophotometry: Passing radiation through a sample (blood in this example), and determining the quantity absorbed. This is further defined as the quantitative measurement of reflection/ transmission of material as a function of the wavelength (λ).

Uses: Fractional saturations – SaO2 (Total Hb, SaO2, haemoglobin derivatives)
Total bilirubin concentration

Haemoglobin (Hb) derivatives include: Oxy-Hb, de-oxy-Hb, Met-Hb, Carboxy-Hb, Fetal Hb.
Haematocrit is determined as a derived measure through the conductivity of the blood sample (this would be applied in ABG analysers without spectrophotometry installed).
The key components of this **optical unit** are: lamp, haemolyser, and the spectrometer.

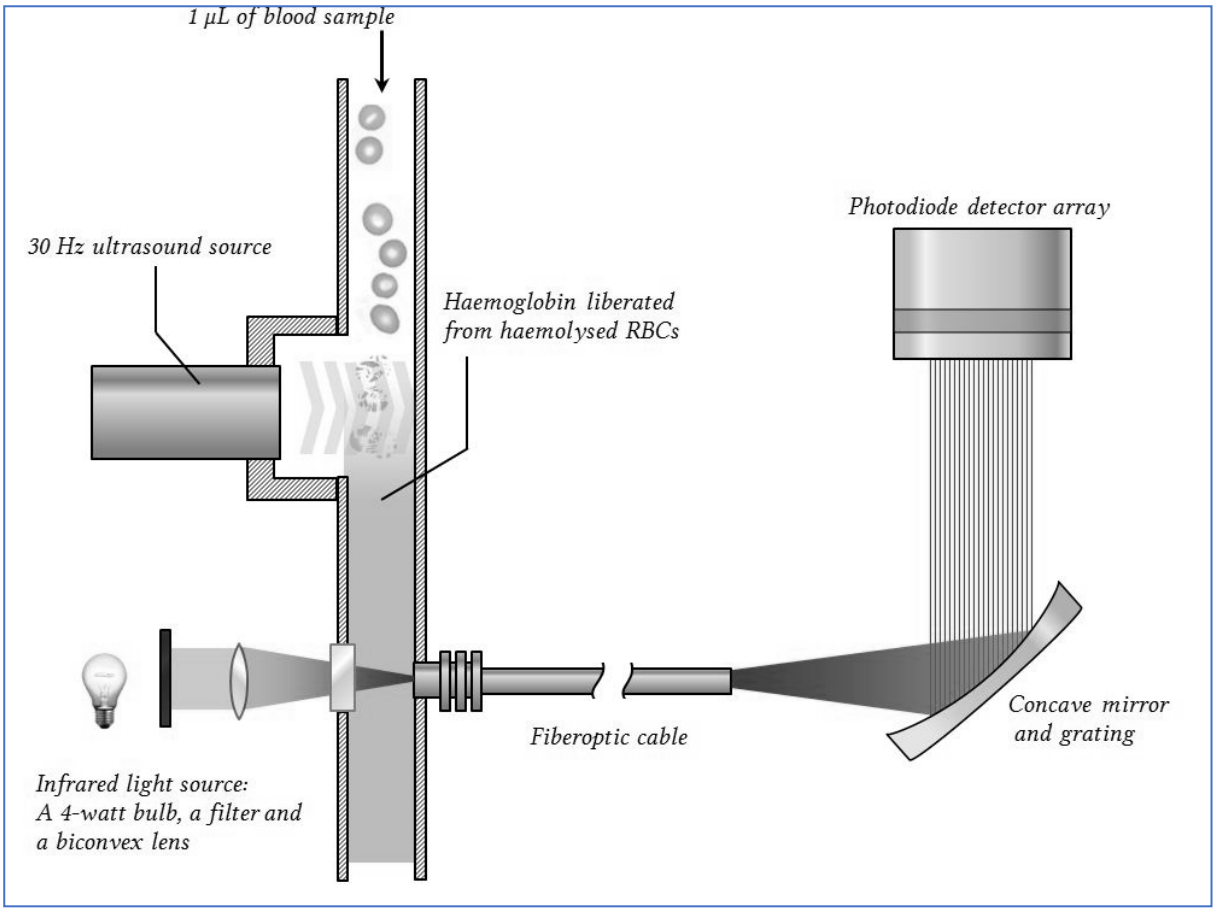
Lamp Unit

Lamp :	This 4W Halogen lamp is the main light source to the unit.
Neon Lamp:	This provides the 585nm (reference) spectral line
Infrared Filter:	Absorbs the heat provided.
Lens:	The lens focuses the light towards the cuvette, which is positioned **within** the "haemolyser" (contains an optical path length of 100 μm).

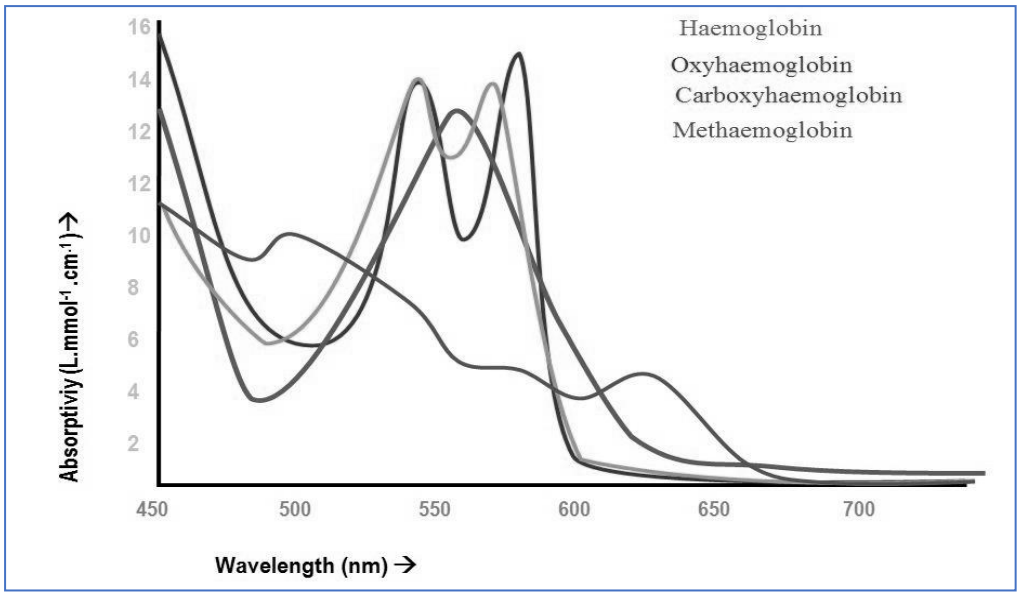
Haemolyser
Ultrasonic resonator emitting ≈ 30kHz. This causes **complete** rupture of the erythrocytes resulting in a homogeneous sample. The pigments are thus completely or evenly distributed across the entire reference range. *(r.b.c.'s do not contain bilirubin, and so a dilution of the sample occurs. This will be mathematically corrected for, prior to "discharge" of the result)*

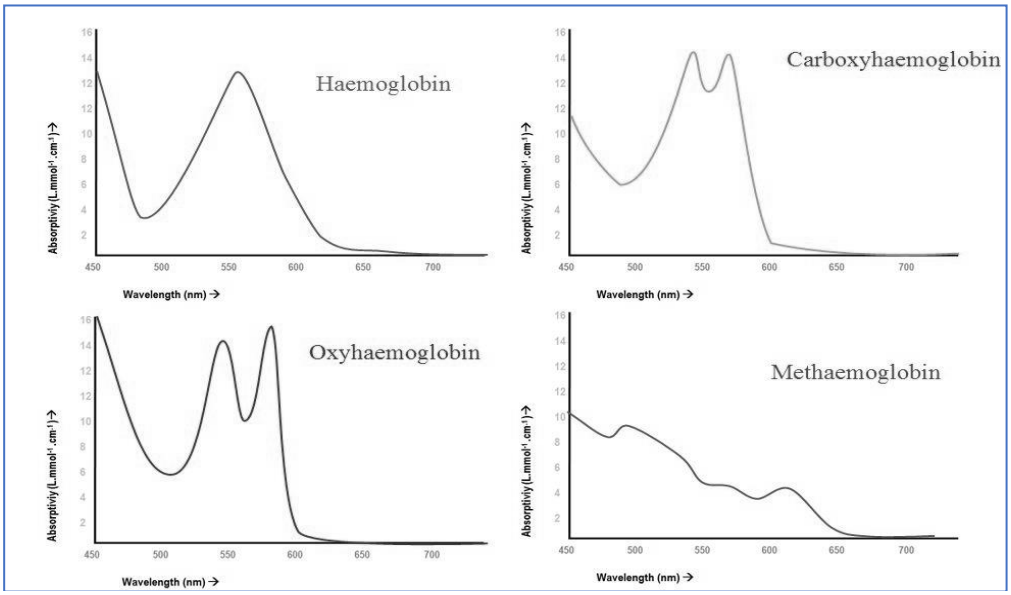
Spectrometer
Wavelength-**specific** photodiodes housed in the spectrometer will measure 128 different λ over 478 – 672 nm. The result is analysed on a recording spectrum.

Beer-Lambert Law (relating the properties of transmitted light to the properties of the substance through which it is transmitted) is applied to determine the amount of this light that is absorbed.



The mechanism and components of the spectrometer





The absorption spectra of the haemoglobin species

Turbidity will significantly affect the accuracy of the specimen measured. The maximum, acceptable level is < 0.5%. It occurs predominantly in samples with very high lipid contact (e.g. Hyperlipidaemia)

CarboxyHaemoglobin (HbCO) – Interesting Numbers		
Cigarettes	Home-life	% HbCO
Non-smokers	Rural	<0.5 %
Non-smoker	Urban	2 %
Smokers		5 – 6 %

% of Total HbCO	Manifestations
10 %	Mild symptoms
30 %	Severe symptoms
60 – 70 %	Respiratory failure (with death imminent)
≥ 80 %	Rapid death

Clinical application of measurement of HbCO

Neonates have a high percentage HbF (fetal haemoglobin) which has a similar structure to HbCO, and HbCO can thus be *falsely* elevated on a neonatal arterial blood gas sample.

Conclusion

Some older references refer to means of measurement that are antiquated, and no longer in use. It is critical to understand the physical principles governing the analysis in our modern day blood gas machines. It is more likely that we will find ourselves **more readily** utilizing in-line arterial blood gas monitors which are non-invasive, reliable, and reproducible (in the near future). These have been highlighted in these notes, and will be further emphasized in the refresher course itself.

Spot ("Easy Reference") Questions

1. Why do we measure ABG?
2. Which values on the ABG are measured by the blood gas machine? Which ABG values are calculated?
3. How is the pH value determined?
4. O_2
    a. How is P_aO_2 determined by the blood gas machine?
    b. What are the alternative names for the O_2 electrode?
5. How is CO_2 determined in the blood gas machine?
6. HCO_3^-
    a. How is HCO_3^- measured?
    b. Compare standard vs. actual HCO_3^-.
    c. What causes changes in actual HCO_3^-? (↑/↓)
7. How is co-oximetry used in ABG machine measurements? List some clinical applications of this (including emergency department, operating theatre, intensive care settings).
8. How accurate is the measurement of ABG Haemoglobin vs a "formal" [Hb]?
9. Base Excess
    a. Define "base excess"(BE).
    b. How is BE calculated? What does it determine?
    c. Define "standard base excess" (SBE). What is its clinical use?
10. Interference with ABG. How do the following impact the results on an ABG:
    a. Excess Heparin
    b. No Heparin
    c. Delay in sample analysis
    d. Air bubbles
    e. Temperature

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Siggaard Anderson vs Stewart

Prof. Ivan Joubert

Depts of Anaesthesia & Perioperative Medicine and Critical Care
University of Cape Town

There has been significant debate in the literature as to the worth of two described approaches to the interpretation of acid-base disturbances. The two contenders are the Siggaard-Anderson approach (based on the calculation of base excess), and the Stewart approach (based on physicochemical principles). So extensive has the discussion on the two approaches been, that it has been dubbed "The great trans-altantic acid-base debate"!

Not to get engaged in the debate that rages, the differences between the two need to be understood.

The Siggaard-Anderson approach is fundamentally based on the calculation of base excess through blood gas analysis. It is a well entrenched method that reliably quantifies both respiratory and metabolic disturbance. Its weakness is the lack of clear mechanistic explanation of metabolic problems. As an example, hyperchloraemic acidosis is well demonstrated through a fall in base excess, but the question of "how" or "why" the pH changes is unaddressed.

The Stewart approach is in no dispute with Siggaard-Anderson, with respect to respiratory acid-base disturbances, but has the capacity of identifying the causative problems in metabolic disturbance. A hyperchloraemic acidosis is both identified and the mechanism explained.

From a practical perspective it is probably useful to make use of both, to obtain the greatest amount of clarity in acid-base disturbances.

The following notes set out to provide essential information for use in the interpretation of metabolic disturbances as encountered in the clinical environment.

As there is no conflict with respect to either the identification or explanation of respiratory disturbances, what follows focuses on metabolic disturbances.

The Stewart approach

Stewart proposed a physicochemical approach to acid base disturbances that relies on a few basic physical principles:

- The law of mass action
- The law of conservation of mass
- The conservation of charge

Stewart explains acid-base disturbances in terms of three fundamental variables:

- The P_{CO_2}
- The strong ion difference
- The total amount of weak non-volatile acid (A_{TOT})

The three variables above, are all independent i.e. abnormalities of their values are the essence of the cause of acid-base disturbances. Variables like pH and base excess are dependant variables. In other words the dependant variables are the end result of changes in the independent variables.

It is interesting to note that for each of Stewart's independent variables there are probably specific physiologic "sensors" and "effectors".

- P_{CO_2} – sensing of pH in the CSF – changes effected by the respiratory system
- Strong ion difference – sensing of chloride transport in the kidney – changes effected by the renal tubules
- ATOT – sensing probably occurs in the liver – changes effected by the liver and kidney

Central to the understanding of the Stewart approach are some of the unique properties that water has. These can be considered as follows:

- Water has a high molar concentration
- Water can be ionised
- Solutes added to water alter the ionisation of water, and hence the pH
    - Note that changes in temperature and pressure can also alter the ionisation of water.

The Siggaard-Anderson approach

This is the approach that most are familiar with. Respiratory abnormalities and their effects on pH are almost intuitive to most; but metabolic abnormalities, though easily identified, are shrouded in mystery.

The definition of pH

pH is defined as the concentration of hydrogen ions expressed as the negative log to base 10.

$$pH = -\log_{10}[H^+]$$

As an abnormality of pH indicates an abnormality of hydrogen ion concentration, interpretation of this variable alone, can only indicate either acidaemia or alkalaemia.

The blood gas analyser

From a pure blood gas perspetive, a blood gas analyser only measures three variables – pH, P_{O_2} and P_{CO_2}. For the purposes of the following discussion, only pH and P_{CO_2} are relevant.

All of the remaining variables are calculated – primarily through manipulation of the Henderson-Hasselbalch equation.

Important concepts for interpreting blood gasses

The Henderson-Hasselbalch equation

This equation expresses the relationship between pH, pK_a and [acid] and [base].

$$pH = pK_a + \log\frac{base}{acid}$$

For blood gas interpretation purposes this equation can be expressed as:

$$pH = pK_a + \log\frac{[HCO_3^-]}{[H_2CO_3]}$$

Or more simply:

$$pH = 6.1 + \log\frac{[HCO_3^-]}{0.03\ PCO_2}$$

Here 0.03 is the solubility coefficient of CO_2 when expressed in mmHg. [0.225 is the solubility coefficient expressed in kPa]. 6.1 is the pK_a of the bicarbonate buffer system.

Bicarbonate

As the blood gas analyser measures pH and P_{CO_2}, the HCO_3 is a calculated variable.

Bicarbonate can only be used to assess a metabolic disturbance if there is no respiratory abnormality!

As a calculated variable, bicarbonate is affected by both respiratory and metabolic disturbances. It cannot, therefore, be an ideal measure of either. Moreover, the relationship between metabolic acidosis and bicarbonate is neither consistent nor linear. Finally, in acid-base determinations the concentration (mEq/L) of bicarbonate ions (HCO_3^-) is not measured, but calculated from P_{CO_2} and pH.

Bicarbonate is therefore not a particularly useful variable – it is merely the product of calculation!

Standard bicarbonate

While bicarbonate itself is a poor measurement of either the respiratory or metabolic regulator, **standard bicarbonate** is a better measurement of the metabolic component.

It was introduced in 1957 by Jorgensen and Astrup. It was defined as the bicarbonate concentration under standard conditions: P_{CO_2}=40 mmHg (5.3kPa), temperature of 37^{o}C, and haemoglobin being fully saturated with oxygen.

As the standard bicarbonate includes correction for any respiratory abnormality, it is useful in the identification of metabolic disturbance.

Base excess

The year after introducing Standard Bicarbonate, Astrup and Siggard-Andersen, in 1958, introduced Base Excess as a better method of measuring the metabolic component. In essence the method calculated the quantity of Acid or Alkali required to return the plasma **in-vitro** to a normal pH under standard conditions (these being P_{CO_2} and temperature).

Standard Base excess

Standard Base Excess is the Base Excess value calculated for anaemic blood (Hb = 5 g/dl) on the principle that this closely represents the behaviour of the whole human being. The rationale for this is that in the whole body, haemoglobin effectively buffers the plasma and the much larger extracellular fluid, i.e., the behaviour is that of anaemic blood. The method predicts the quantity of Acid or Alkali required to return the plasma **in-vivo** to a normal pH under standard conditions.

In the clinical arena, if standard base excess is available, it represents the **best** measure of the metabolic disturbance.

Assessing metabolic disturbance

From above it is appreciated that base excess and standard base excess can be used to identify metabolic disturbance. Remember that respiratory abnormalities are excluded in these calculations.

Nevertheless, neither of the above can explain the mechanism of any metabolic disturbance. Metabolic disturbance can only be explained through the calculation of anion gap, or better through the appreciation of strong ion difference and total ionised protein.

The Anion gap

This is calculated as:

$$Anion\ gap = [Na^+ + K^+] - [Cl^- + HCO_3^-]$$

The anion gap is only useful in the description of metabolic acidosis, where it is classified as either being increased, or decreased.

The causes of a raised anion gap acidosis are:

- Lactic acidosis
- Ketoacidosis
- Chronic renal failure (accumulation of sulphates, phosphates, uric acid)
- Intoxication or drug overdose, e.g., ethanol, methanol, ethylene glycol, formaldehyde, paraldehyde, salicylates, INH, toluene, sulphates, metformin.
- Rabdomyolysis

The causes of a normal anion gap acidosis (mostly associated with a Cl^- abnormality) are:

- Longstanding diarrhoea (bicarbonate loss)
- Uretero-sigmoidostomy
- Pancreatic fistula
- Renal Tubular Acidosis
- Intoxication, e.g., ammonium chloride, acetazolamide, bile acid sequestrants

Strong ion difference

The Strong Ion Difference is the difference between the sums of concentrations of the strong cations and strong anions:

$$[SID] = [Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] - [Cl^-] - [\text{Other Strong Anions}]$$

Lactate is a strong anion and should be considered in the above equation.

Strong ions are always completely dissociated in solution. Note that bicarbonate is not a strong ion at all!

The normal strong ion difference is about 35. Any departure from this number is roughly equivalent to the SBE.

The primary reason that alterations in strong ion concentration affect pH is that the ionisation of water is altered.

Weak non-volatile acids - [A_{TOT}^-]

[A_{TOT}] is the total plasma concentration of the weak non-volatile acids, inorganic phosphate, serum proteins, and albumin.

$[A_{TOT}] = [Pi_{TOT}] + [Pr_{TOT}]$ + albumin.

Proteins provide a significant source of ionisable substrate that is useful in the buffering of acid-base disturbances. A low albumin plays an alkalinising role from an acid-base perspective.

The use of the strong ion difference and abnormalities of A_{TOT}^- can provide additional insight into the appreciation of the cause of an acid-base disturbance.

Clinical considerations

Changes in acid-base status are either respiratory or non-respiratory, i.e., metabolic:

Respiratory:

The effects of changes of P_{CO_2} are well understood and produce the expected alterations in [H^+]:

$$CO_2 + H_2O <—> H_2CO_3 <—> HCO_3^- + H^+$$

Metabolic (Non-Respiratory):

Metabolic disturbances, cannot be viewed as a consequence of bicarbonate concentration because bicarbonate is merely a dependent variable. The two possible sources of metabolic, i.e., non-respiratory disturbances, are either [SID] or [A_{TOT}], or both.

With normal protein levels, [SID] is about 40mEq/L. Any departure from this normal value is roughly equivalent to the standard base excess (SBE), i.e., if the measured [SID] were 45 mEq/L, the BE would be about 5 mEq/L, and a measured [SID] of 32 mEq/L would approximate to a BE = -8 mEq/L. Because [SID] does not allow for haemoglobin, there is often a small discrepancy.

Changing [SID]:

[SID] can be changed by two principal methods:

1) Concentration:
   Dehydration or over-hydration alters the concentration of the strong ions and therefore increases, or decreases, any difference. The body's normal state is on the alkaline side of neutral. Therefore, dehydration concentrates the alkalinity (contraction alkalosis) and increases [SID]; whereas, over-hydration dilutes this alkaline state towards neutral (dilutional acidosis) and decreases [SID].
2) Strong Ion Changes:
   If the sodium concentration is normal, alterations in the concentration of other strong ions will affect [SID]:
   a. Inorganic Acids:
      The only strong ion capable of sufficient change is chloride, (potassium, calcium and magnesium do not change significantly). An increased Cl^- concentration causes an acidosis and a decreased [SID] – hyperchloraemic acidosis. Because the chloride ions are measured, the anion gap will be normal.
   b. Organic Acids:
      By contrast, if the body accumulates one of the organic acids, e.g., lactate, formate, keto-acids, then the metabolic acidosis is characterized by a normal chloride concentration and an abnormal anion gap because of the presence of the "unmeasured" organic acid.

Changing [A_{TOT}^-]:

The non-volatile weak acids comprise inorganic phosphate, albumin and other plasma proteins. Making the greatest contribution to acid-base balance are the proteins, particularly albumin, which behave collectively as a weak acid.

Hypoproteinaemia, therefore, causes a base excess and vice versa.

Phosphate levels are normally so low that a significant fall is impossible. However, in renal failure, high phosphate levels contribute to the acidaemia.

Interpreting acid-base derangement

The initial inspection of pH, P_{CO_2} and SBE are likely to be most helpful.

Simple respiratory acidosis is easy to identify, most commonly resulting from a depression of minute ventilation, for a variety of reasons. The SBE is normal.

Respiratory alkalosis is relatively rare. Hyperventilation is an unusual physiologic disturbance that may be secondary to hypoxia (with no depression of minute ventilation), high altitude or unusual drive of the respiratory centre. Once again the SBE is normal.

Interpreting metabolic disturbance is best done through the inspection of SBE, thus discounting any respiratory component of the disturbance to pH.

For metabolic acidosis further insight is gained through the use of anion gap, or SID and $[A_{TOT}^-]$.

Primary metabolic alkalosis may occur for a variety of reasons:

- Loss of acid via: Urine, stools, or vomiting
- Transfer of hydrogen ions into the cells
- Excessive bicarbonate administration, e.g. alkali given to patients with renal failure.
- Contraction of the extracellular space due to excessive diuretic treatment

Simple mathematics!

As a rule of thumb the following holds true:

P_{CO_2}	pH	HCO_3^-
12 mmHg 1.6 kPa	0.1	6 mEq/l

The equation means that a change of 0.1 in the pH can be caused by either:

1. A respiratory change (P_{CO_2} change) of 12 mmHg, or
2. A metabolic change (Base Excess change) of 6 mEq/L.
3. A mixture of the two.

This relationship allows the components to be "added" and "subtracted". For example, a pH of 7.2 (0.2 more "Acid") can be caused by:

1. a P_{CO_2} of 64 with a BE = 0 mEq/L
2. a P_{CO_2} of 52 with a BE = -6 mEq/L
3. a P_{CO_2} of 40 with a BE = -12 mEq/L
4. a P_{CO_2} of 32 with a BE = -18 mEq/L

Although this relationship is an approximation, it provides acceptable clinical results in most circumstances; its real value is in granting insight and understanding.

Identifying compensation

Compensation for acid-base disturbances is never complete from a mathematical perspective. In other words the pH can never be brought back to 7.4 by physiologic means. Compensation may be complete in that physiology has done all it can to offset the disturbance. At best complete physiologic compensation will lie roughly halfway between full mathematical compensation, and no compensation.

Conclusion

Acid-base interpretation is easy!

- Identify an acidaemia or alkalaemia
  - If pH is within the normal range in the face of significant respiratory and metabolic disturbance, it might be more complex! Compensation is never mathematically complete.
- Then look at P_{CO_2} and SBE.
  - Start to identify either respiratory or metabolic causes of the disturbance
- For metabolic acidosis
  - Consider both the anion gap and SID for insight
- Consider SID and $[A_{TOT}^-]$ for all metabolic disturbances
- Use the rule of thumb relationship to help predict necessary compensation.
- For the last time – remember that compensation is never mathematically complete – usually only half compensation is possible.

Notes:

An Approach to Blood Gas Interpretation

Dr Marcin Nejthardt

Dept of Anaesthesia & Perioperative Medicine
University of Cape Town

Step 1 – P_{O_2}

Consider:
Is the *blood gas* taken from a patient on room air or supplemental oxygen?
Is the *blood gas* an arterial or a venous sample?

The above two are important to determine if hyper or hypoxaemia is present.

Hypoxaemia is defined as P_aO_2 < 8 kPa (60 mmHg).

Hypoxia on the other hand is a low oxygen content in tissue and has a number of causes and can be classified as:

1. Hypoxic (high altitude, low F_IO_2, V / Q mismatch, diffusion abnormality)
2. Anaemic (low Hb, carbon monoxide poisoning)
3. Stagnant (low cardiac output)
4. Histotoxic (inability of cells to utilize oxygen due to mitochondrial dysfunction eg. cyanide, inflammatory conditions (sepsis), neuro-inflammatory conditions (Alzheimer's, Parkinson's, multiple sclerosis) and ischaemia related reperfusion injury.

What is a normal P_{O_2}?
This will depend on:

1. Sampling site: P_aO_2 (arterial) or P_vO_2 (venous)
   i. Mixed venous refers to the sample of blood from the Pulmonary Artery.
   ii. Central venous sample refers to blood drawn from the Internal Jugular or Subclavian Veins.
   iii. P_{O_2} will be lowest in a mixed venous sample, followed by the central venous sample and finally from a peripheral vein eg. cubital fossa vein.
2. Altitude: The greater the altitude, the lower the partial pressure. Johannesburg at an altitude of 1 700 m has an atmospheric pressure of 83 kPa (622 mmHg).

P_aO_2 Normal Value kPa (mmHg)	Room air	40% facemask	100% via ETT	Saturation (%)
- Sea level				
P_aO_2	13.3(100)	32(240)	88(660)	97-100
P_vO_2	5.3 (40)		6.7(50)	75 - 83
- Johannesburg (1700m)				
P_aO_2	10.3(77)	25(187)	71(530)	95-100
P_vO_2	4.7(35)		6(45)	73-81

What is the **Alveolar–arteriolar (A-a) gradient**?

$$A\text{–}a\ gradient = P_AO_2 - P_aO_2$$

$$A - a\ gradient = [F_i(P_{atm} - P_{H_20}) - \frac{P_{ACO_2}}{R}] - P_aO_2$$

where: F_i = fraction inspired oxygen
P_{atm} = atmospheric pressure
P_{H_20} = Partial pressure of fully saturated water vapour at 37°C [6.3kPa(47mmHg)]
R = Respiratory quotient. Depends on food source used for metabolic respiration. Typical value of 0.8
P_aO_2 = the measure PO_2 from an arterial blood gas

Normal A-a gradient is generally less than 2 kPa (15 mmHg) irrespective of altitude but does gradually increases with age.

An increased A-a gradient suggests a V/Q mismatch, diffusion abnormality or right to left shunt.

Note: Under normal physiological conditions (normal extraction of 5 mlO_2/100ml blood) adding supplemental oxygen has very little effect on increasing P_vO_2 (mixed venous saturation of 75% equates to PO_2 5.3 kPa(40 mmHg) as per O_2-Hb dissociation curve).

A problem with tissue extraction may result in mixed venous saturation rising to >90% with a subsequent P_vO_2 rising to a higher level and approaching P_aO_2 levels.

Step 2 – pH

Normal pH: 7.36 - 7.44

If pH < 7.36 = acidaemia
> 7.44 = alkalaemia

Step 3 – PCO_2

This is to assess the respiratory contribution to the pH.
Normal P_aCO_2 (arterial)
P_vCO_2 (venous)

PCO_2	Room air
Normal Value kPa (mmHg)	
- Sea level	
P_aCO_2	5.3 (40)
P_vCO_2	6.0 (45)
- Johannesburg (1700 m)	
P_aCO_2	4.7 (35)
P_vCO_2	5.3 (40)

Note:
1. Main adaptation to altitude is increased minute ventilation hence lowering PCO_2.
2. Lower PO_2 directly increases PCO_2 (Haldane effect)
3. Increasing F_IO_2 has two effects on PCO_2
   a. Decrease in respiratory drive increases PCO_2
   b. Decreases binding to haemoglobin and decreases PCO_2 (Haldane effect)
4. A venous or arterial blood gas are reasonable at assessing a patient's CO_2

If elevated – respiratory acidosis
If decreased – respiratory alkalosis

Step 4 – Metabolic contribution to pH

Use ***standard base excess***, ***anion gap, strong ion difference*** *and* ***[A_{TOT}]*** to evaluate the metabolic component.

Lactate is a strong ion and thus forms part of the strong ion calculation and interpretation.

Normal values:

Standard base excess	= -2 to +2 mEq/L
Anion gap	= 8 - 16 mEq/L
Strong ion difference	= 35 - 45 mEq/L
[A_{TOT}]	= 14 - 17 mEq/L
Lactate	= 0.5 - 1 mmol/L

Step 5 – Is there any compensation?

Interpret the *blood gas* in the clinical context.
Compensation never brings the pH back to normal range. If there is a normal pH in the face of obvious respiratory or metabolic disturbance then a mixed acid-base disturbance is present.

It is important to consider the blood gas in the context of the clinical scenario. Determining the adequacy of compensation can be attempted through a number of empirically developed formulae.

One such is *Winter's Formula* to assess the expected change in CO_2 for a given metabolic acidosis

Metabolic Acidosis: (The One & a Half plus 8 Rule)
The expected P_{CO_2} (in mmHg) is calculated from the following formula:
Expected $P_{CO_2} = 1.5 \times [HCO_3^-] + 8$ (range: +/- 2)

Other formulae include:

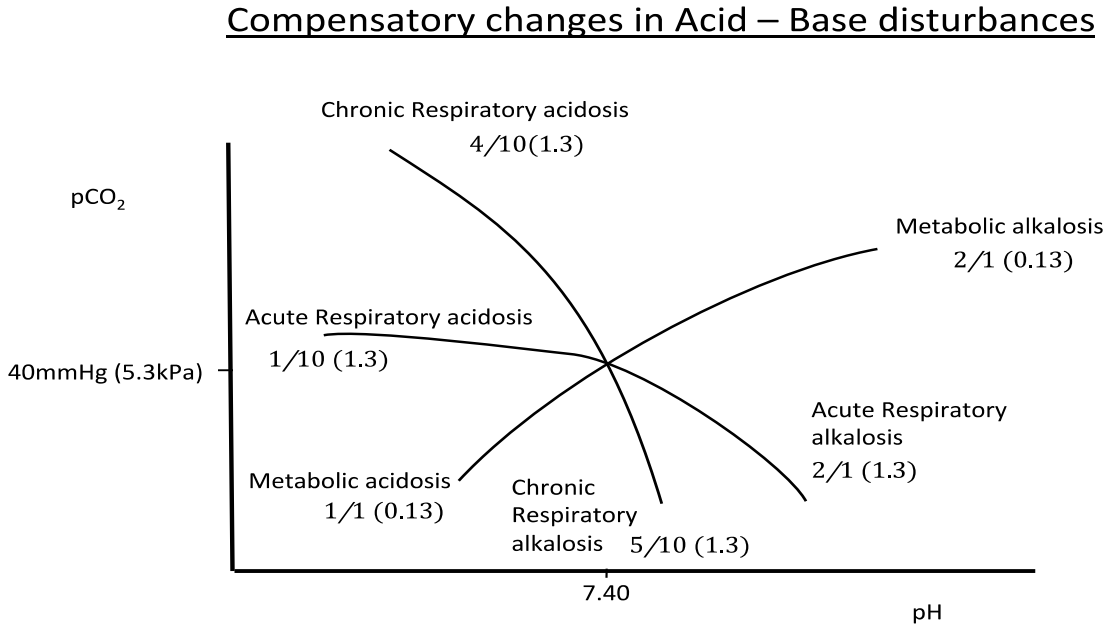
Acute Respiratory Acidosis: (The 1 for 10 Rule)
The $[HCO_3]$ will increase by 1 mmol/l for every 10 mmHg elevation in P_{CO_2} above 40 mmHg.
Expected $[HCO_3^-]$ = 24 + {(Actual P_{CO_2} - 40) / 10}

Chronic Respiratory Acidosis: (The 4 for 10 Rule)
The $[HCO_3^-]$ will increase by 4 mmol/l for every 10 mmHg elevation in P_{CO_2} above 40mmHg.
Expected $[HCO_3^-]$ = 24 + 4 {(Actual P_{CO_2} - 40) / 10}

Acute Respiratory Alkalosis: (The 2 for 10 Rule)
The $[HCO_3^-]$ will decrease by 2 mmol/l for every 10 mmHg decrease in P_{CO_2} below 40 mmHg. Expected $[HCO_3^-]$ = 24 - 2 {(40 - Actual P_{CO_2}) / 10}

Chronic Respiratory Alkalosis: (The 5 for 10 Rule)
The $[HCO_3^-]$ will decrease by 5 mmol/l for every 10 mmHg decrease in P_{CO_2} below 40 mmHg. Expected $[HCO_3^-]$ = 24 - 5 {(40 - Actual P_{CO_2}) / 10} (range: +/- 2)

Metabolic Alkalosis: (The Point Seven plus Twenty Rule)
The expected P_{CO_2} (in mmHg) is calculated from the following formula:
Expected $P_{CO_2} = 0.7 [HCO_3^-] + 20$ (range: +/- 5)



A visual representation of the compensatory changes in acid-base disturbances. The numerator indicates the change in $[HCO_3^-]$ in mmol/l whilst the denominator indicates the change in P_{CO_2} in mmHg and (kPa). For ease of recall the metabolic compensations have been modified.

These unfortunately are not intuitive and difficult to commit to memory especially at the bedside.

An easier bedside approach may be to use the following approximations (see I Joubert ARC 2017,18)

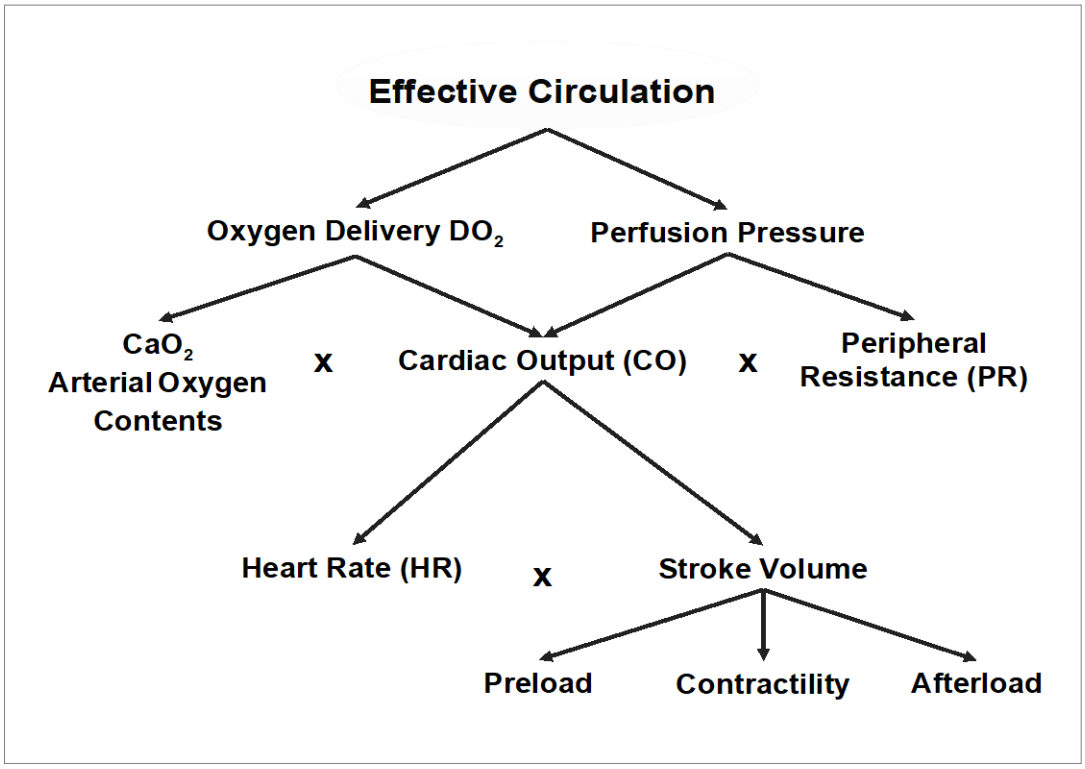
PCO_2	pH	HCO_3^-
12 mmHg	0.1	6 mEq/l
1.6 kPa		

Understanding the primary disturbance from the clinical scenario would point to the expected compensatory mechanism. Compensation is never complete (returning the pH back to a normal range). *Expected (appropriate) compensation* in clinical practice returns the pH to about halfway to normal.

The Cardiac Cycle
The "Wiggers diagram"

Prof. Justiaan Swanevelder

Dept of Anaesthesia & Perioperative Medicine
University of Cape Town



Each cardiac cycle consists of a period of relaxation (diastole) followed by ventricular contraction (systole). During diastole the ventricles are relaxed to allow filling. In systole the right and left ventricles contract, ejecting blood into the pulmonary and systemic circulations respectively.

Ventricles

The left ventricle pumps blood into the systemic circulation via the aorta. The systemic vascular resistance (SVR) is 5–7 times greater than the pulmonary vascular resistance (PVR). This makes it a high-pressure system (compared with the pulmonary vascular system), which requires a greater mechanical power output from the left ventricle (LV). The free wall of the LV and the interventricular septum form the bulk of the muscle mass in the heart. A normal LV can develop intraventricular pressures up to 300 mmHg. Coronary perfusion to the LV occurs mainly in diastole, when the myocardium is relaxed.

The right ventricle receives blood from the venae cavae and coronary circulation, and pumps it via the pulmonary vasculature into the LV. Since PVR is a fraction of SVR, pulmonary arterial pressures are relatively low and the wall thickness of the right ventricle (RV) is much less than that of the LV. The RV thus resembles a passive conduit rather than a pump. Coronary perfusion to the RV occurs continuously during systole and diastole because of the low intraventricular and intramural pressures.

In spite of the anatomical differences, the mechanical behaviour of the RV and LV is very similar.

The cardiac cycle can be examined in detail by considering the ECG trace, intracardiac pressure and volume curves, and heart valve function.

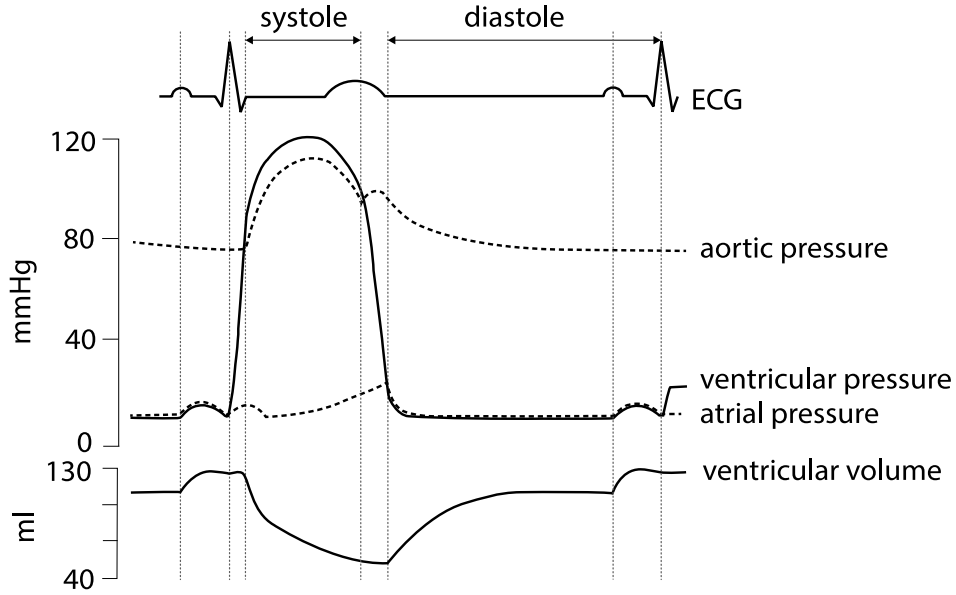


Fig. 1 The "Wiggers Diagram" - Cardiac cycle, showing ventricular volume, ventricular pressure, aortic pressure and atrial pressure

Systolic function

Systole can be broken down into the following stages:

- Isovolumetric ventricular contraction
- Ventricular ejection

Systole commences with a period of isovolumetric contraction initiated by the QRS complex of the ECG. During this brief period the volume of the ventricle does not change since both the AV and semilunar valves are closed. Isovolumetric contraction ends when the semilunar valve opens and ejection begins. The events during systole are described below and should be considered along with the ventricular pressure, aortic pressure and ventricular volume curves.

Left ventricular pressure
The QRS complex of the ECG initiates ventricular contraction. As the pressure in the left ventricle increases during isovolumetric contraction, it comes to exceed the pressure in the aorta. At this point the aortic valve opens and ejection begins. The aortic valve opens at about 80 mmHg. Ejection continues as long as ventricular pressure exceeds aortic pressure. The total volume ejected into the aorta is the stroke volume (SV). The ventricular pressure increases initially during ejection, but then starts to decrease as the ventricle relaxes. The gradient between ventricle and aorta starts to reverse at this point, since LV pressure has started to fall but aortic pressure is maintained by the momentum of the last of the ejected blood. When the ventricular to aortic pressure gradient has reversed, the aortic valve closes and isovolumetric relaxation begins. The dicrotic notch on the aortic pressure curve (below) marks this point. The LV pressure normally reaches a systolic maximum of 120 mmHg. At the end of systole the LV pressure is described as the end-systolic pressure and the LV volume is at its smallest (end-systolic volume), about 40–50 ml.

Right ventricular pressure
This follows a similar course to LV pressure. The tricuspid and pulmonary valves dictate events, with ejection occurring into the pulmonary artery. Right ventricular pressure reaches a maximum of about 20–24 mmHg during systole.

Ventricular volume
Diastole commences in the left side of the heart with closure of the aortic valve and relaxation of the left ventricle. Since the mitral and aortic valves are both closed at this time the relaxation is described as isovolumetric. The ventricle contains 40–50 ml blood at this stage (end-systolic volume).

Isovolumetric relaxation ends with opening of the mitral valve, when a period of rapid filling of the ventricle begins, which lasts for the first third of diastole. After the initial period of rapid filling follows a period of passive filling called diastasis and flow continues passively into the ventricle, providing up to 75% (60 ml) of the filling volume. During the last third of diastole the P wave of the ECG initiates atrial contraction, which contributes the remaining 25% of filling to give an end-diastolic volume of about 120 ml. The end-diastolic volume of the ventricle is not always 120 ml, but can vary due to changes in venous return to the heart, contractility and heart rate. A similar sequence of events occurs on the right side of the heart, controlled by the pulmonary and tricuspid valves.

Aortic pressure curve
Ejection of blood into the aorta begins when the aortic valve opens. During ejection, the aortic pressure follows the ventricular pressure curve with a small pressure gradient of about 1–2 mmHg when the aortic valve is normal. As ejection proceeds aortic pressure increases to a maximum (systolic pressure) and starts to fall as the LV relaxes. When the ventricular pressure has fallen below the aortic pressure, the aortic valve closes and ejection ceases. Following closure of the aortic valve, elastic rebound of the aorta walls gives rise to a small hump in the aortic pressure curve forming the dicrotic notch. This notch marks the beginning of diastole. During diastole the aortic pressure gradually falls to a minimum (diastolic pressure), due to runoff of blood to the systemic circulation.

Atrial pressure
Normally blood fills the right atrium (RA) via the superior and inferior venae cavae, continuously throughout the cardiac cycle. This flow is returned from the peripheral circulation and is called the venous return to the heart. On the left side of the heart, the left atrium (LA) receives blood from the pulmonary vascular bed via the pulmonary veins.
Passive filling of the atria produces RA pressures of 0–2 mmHg and LA pressures of 2–5 mmHg. During diastole atrial pressures follow ventricular pressures since the AV valves are open and the two chambers are joined. Three waves or peaks are produced in the atrial pressure curve during the cycle. At the end of diastole the atria prime the ventricles by contracting and developing pressures between 0 and 5 mmHg. Atrial contraction is shown on the atrial pressure curve as a smooth peak immediately preceding systole, the 'a' wave. As systole begins the AV valves close and a brief period of isovolumetric contraction occurs, producing a second low-pressure peak, the 'c' wave. This is due to the AV valve bulging back into the atrium.
As blood is ejected during systole the atrium continues to fill with the AV valve closed and atrial pressure increases until early diastole when the AV valve opens. At this point rapid filling of the ventricles commences and a sudden fall in atrial pressure follows. This gives rise to the 'v' wave.

Diastolic function

Diastole can be broken down into the following stages:

- Isovolumetric ventricular relaxation
- Rapid ventricular filling
- Slow ventricular filling (diastasis)
- Atrial contraction

Although diastole appears to be a passive part of the cardiac cycle, it has some important functions:

- Myocardial relaxation – a metabolically active phase. One essential process is the reuptake of calcium by the sarcoplasmic reticulum. Incomplete reuptake leads to diastolic dysfunction due to decreased end-diastolic compliance. The negative slope of the ventricular pressure–time curve during isovolumetric relaxation (termed dP/dt(max)) indicates myocardial relaxation. Increased sympathetic tone or circulating catecholamine levels give rise to an increased dP/dt(max). This is known as positive lusitropy.
- Ventricular filling – provides the volume for the cardiac pump. Most of the ventricular filling occurs during early diastole. There is only a small increase in ventricular volume during diastasis. As the heart rate increases diastasis is shortened first. When the heart rate exceeds about 140 bpm, rapid filling in early diastole becomes compromised and the volume of blood ejected during systole (stroke volume, SV) is significantly decreased.
- Atrial contraction – contributes up to 25% of total ventricular filling in the normal heart. This atrial contribution can become of greater importance in the presence of myocardial ischaemia or ventricular hypertrophy.
- Coronary artery perfusion – the greater part of left coronary blood flow occurs during diastole.

Cardiac valves

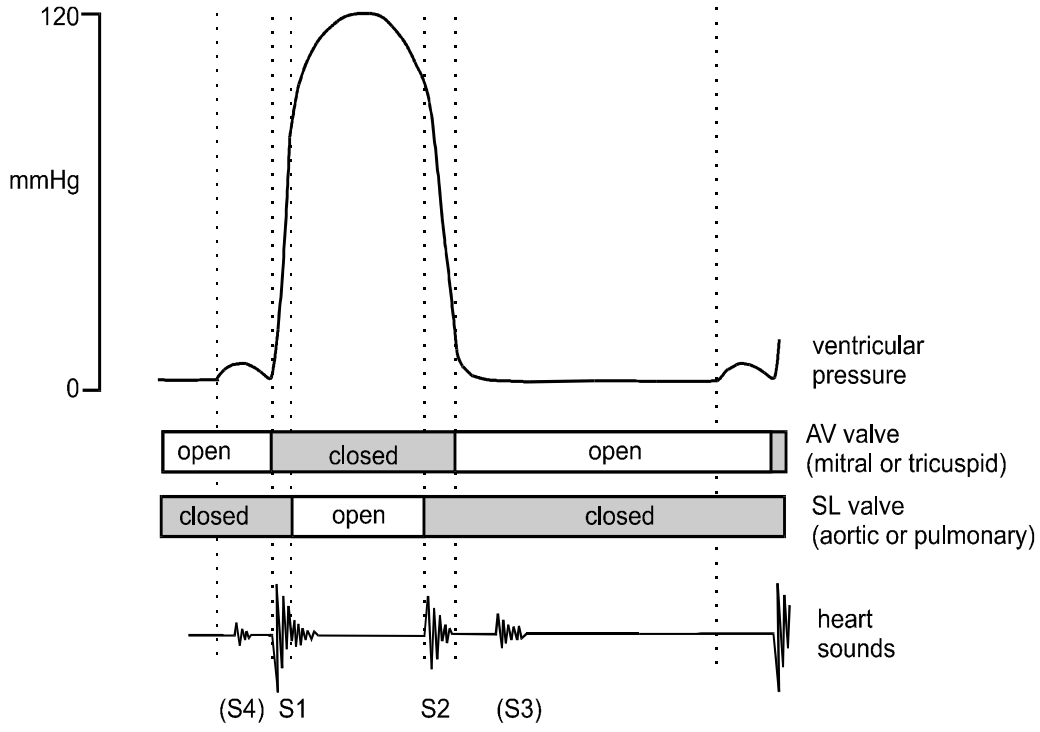
The cardiac valves open and close passively in response to the changes in pressure gradient across them. These valves control the sequence of flow between atria and ventricles, and from the ventricles to the pulmonary and systemic circulations. Valve timing in relation to the ventricular pressure curve is shown in Fig 2.

The AV valves are the mitral and tricuspid valves. These prevent backflow from the ventricles into the atria during systole. The papillary muscles are attached to the AV valves by chordae tendineae. They contract together with the ventricular muscle during systole, but do not help to close the valves. They prevent excessive bulging of the valves into the atria and pull the base of the heart toward the ventricular apex to shorten the longitudinal axis of the ventricle, thus increasing systolic efficiency.

The semilunar (SL) valves are the aortic and pulmonary valves. These prevent backflow from the aorta and pulmonary arteries into the ventricles during diastole. The SL valves function quite differently from the AV valves because they are exposed to higher pressures in the arteries. They are smaller (normal aortic valve area is 2.6–3.5 cm^2 while normal mitral valve area is 4–6 cm^2), and therefore the blood velocity through them is greater.

Disease in the cardiac valves may cause them to leak when they are meant to be closed, thus allowing backflow or regurgitation. This situation leads to inefficiency in producing cardiac output (CO), since the work done by the heart has to increase to compensate for the backflow and yet maintain adequate CO. Mitral and aortic regurgitation are the most common regurgitant lesions.

Alternatively, the orifice of a valve may become narrowed or stenotic. This obstructs the flow of blood through it and requires increased pressure gradients to be generated across the valve to achieve adequate blood flows. In mitral stenosis the valve area can be reduced by >50%. This causes the left atrium to contract more forcefully to maintain ventricular filling. In severe cases a valve area of 1 cm^2 can require the left atrium to produce peak pressures of 25 mmHg to produce normal CO. Aortic stenosis obstructs left ventricular output and increases the workload of the left ventricle. The stenosis can multiply the normal pressure gradient across the aortic valve during systole by 10 times or more. When the aortic valve area decreases by 70% (<0.8 cm^2), the stenosis becomes critical and systolic pressure gradients across the valve of >50 mmHg may be required to produce normal systemic pressures.



Fig, 2. Heart sounds, valves, and timing

Differences in timing between left and right sides of the heart

Although the sequence of events on each side of the heart is similar, events occur asynchronously. This disparity in timing reflects differences in anatomy and working pressures between left and right sides of the heart. RA systole precedes LA systole; however, RV contraction starts after LV contraction. In spite of contracting later, the RV starts to eject blood before the LV because pulmonary artery pressure is lower than aortic pressure. Differences of timing also occur in the closure of the heart valves. These differences in valve timing lead to 'splitting' of the heart sounds.

Heart sounds and murmurs

In the normal individual two heart sounds can be heard during each cardiac cycle. They are produced by closure of the valves, which causes the ventricular walls and valve leaflets to vibrate, and also produces turbulence of the interrupted blood flow. The first sound (S1) occurs when the AV valves close at the start of ventricular systole and is best heard over the apex of the heart. The mitral valve normally closes earlier than the tricuspid by 10–30 ms. Thus S1 is split, with the mitral component occurring before the tricuspid component. The second sound (S2) corresponds to closure of the SL valves and is heard at the beginning of diastole. During inspiration the aortic valve closes before the pulmonary valve due to increased venous return, which delays RV ejection. During expiration aortic and pulmonary valve closure is simultaneous, and S2 appears to be a single sound. S2 is louder when the diastolic pressure is elevated in the aorta or pulmonary artery.

Abnormal heart sounds can be heard under pathological conditions. Heart failure can cause a third heart sound (S3) to be heard in mid-diastole. This is due to rapid filling of a dilated non-compliant ventricle following the opening of the AV valves. In conditions where stronger atrial contraction develops to help ventricular filling, a fourth heart sound (S4) may occur immediately before S1 (systole). This is thought to be due to ventricular wall vibration in response to forceful atrial filling.

When the cardiac valves undergo pathological changes abnormal sounds called murmurs can sometimes be heard. Under normal conditions blood flow is not turbulent but remains laminar up to a critical velocity. When blood flows across a narrowed valve, flow velocities are higher and turbulent, giving rise to a murmur. In the case of a 'leaking' or incompetent valve, turbulent regurgitant flow is produced, which also creates a murmur. The most common murmurs occur due to faults in the mitral and aortic valves. The valve involved and the type of lesion (stenotic or regurgitant) can be identified by the timing of the murmur and the site on the chest wall where it is loudest. In normal individuals without cardiac disease (especially children) soft physiological systolic murmurs can often be heard.

Central venous pressure

Central venous pressure (CVP) is usually monitored in the large veins feeding the superior vena cava, i.e. the internal jugular or subclavian veins. The CVP waveform reflects right atrial pressure, and therefore consists of 'a', 'c' and 'v' waves that correspond to atrial contraction, isovolumetric contraction and opening of the tricuspid valve, as described above. There are also two labelled downward deflections, the 'x' and 'y' descents, which occur after the 'c' and 'v' waves respectively. The 'x' descent reflects the fall in right ventricular pressure when the pulmonary valve opens. The 'y' descent corresponds to the initial drop in atrial pressure caused by rapid ventricular filling when the AV valves open. Various pathological conditions affect mean CVP or alter the CVP waveform. For example, if the timing of atrial and ventricular contraction become dissociated (as in 3° block) the right atrium contracts against a closed tricuspid valve and produces prominent or 'cannon' 'a' waves.

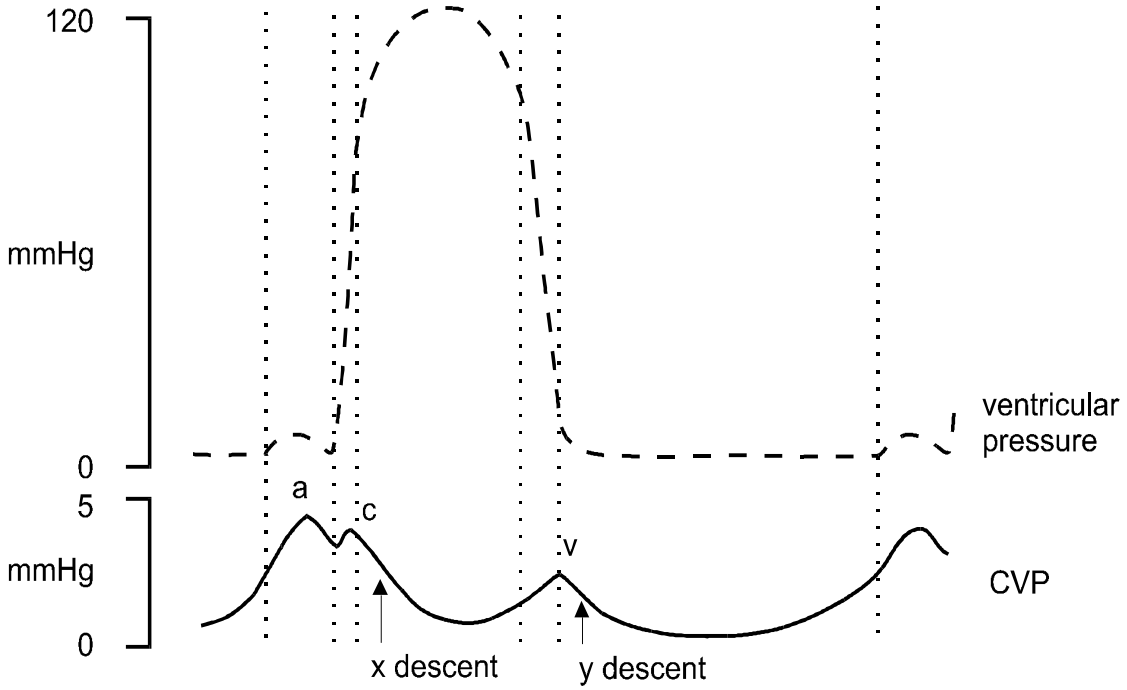


Fig. 3. Central venous pressure waveform

Arterial Transducers and Damping

Dr. Gareth Davies
Department of Anaesthesia
Paarl Hospital

Introduction

A transducer is a device that converts one form of energy to another form of energy. When measuring intra-arterial blood pressure, the arterial pulse pressure mechanical waveform is transmitted via a column of fluid in the arterial catheter and tubing to a pressure transducer, where it is converted into an electrical signal (hydraulic coupling). This signal is then processed, amplified and converted into a visual display by a microprocessor.

The apparatus required for measuring intra-arterial blood pressure includes the following components:

- Intra-arterial catheter
- Fluid filled tubing
- Pressure Transducer
- Infusion/flushing system
- Signal processor, amplifier and display

Basic Principles

A wave is a disturbance that travels through a medium, transferring energy, but not matter. The simplest wave form is the sine wave.

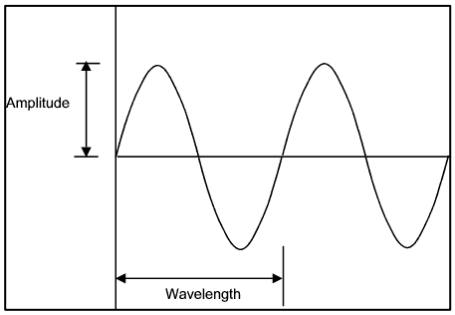


Fig 1: The sine wave

The following key terminology can be used to describe a sine wave:

- *Amplitude*: the maximal displacement from zero
- *Frequency*: the number of cycles per second – expressed as Hertz (Hz)
- *Wavelength*: the distance between two points on the wave that have the same value
- *Phase*: the displacement of one wave in comparison to another

Sine waves are fundamentally important when considering arterial transducers, as any waveform may be represented by combining together sine waves of different frequencies, amplitudes and phases. Thus the complex arterial pulse pressure wave can be broken down into a number of different sine waves (**Fourier analysis**).

This wave consists of a fundamental wave (the pulse rate) and a series of other harmonic waves. These smaller waves have frequencies that are multiples of the fundamental wave (e.g. 2 Hz, 3 Hz, etc.).

A microprocessor performs the function of breaking down the complex waveform into the fundamental wave and at least 10 or more harmonics of higher frequency, to give an accurate representation of the original waveform.

The figures below demonstrate this analysis with two sine waves:

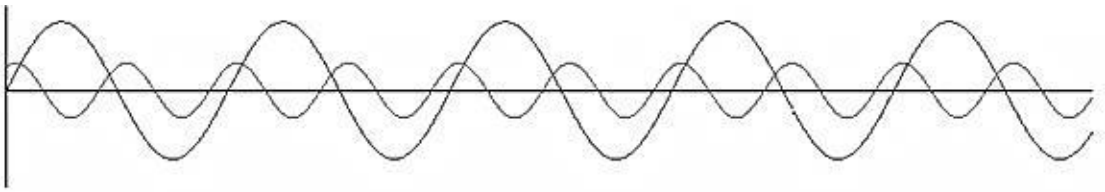


Fig 2: Two sine waves with differing frequency, amplitude and phase

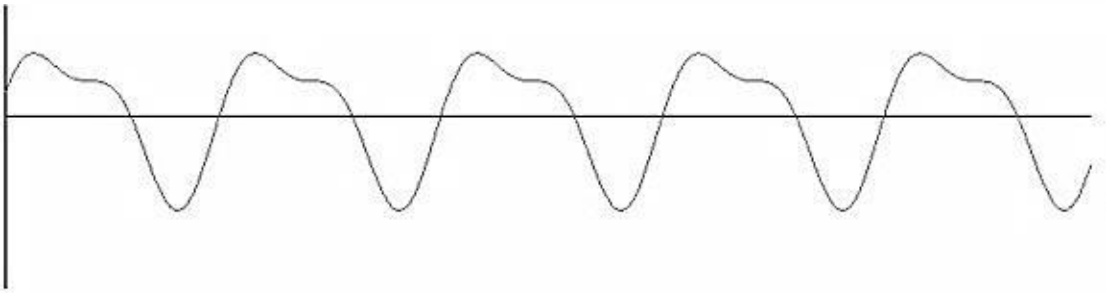


Fig 3: The sum of the two sine waves

Natural frequency and resonance

All materials have a frequency at which they oscillate freely – this is called their *natural frequency*. When a force with a similar frequency to the natural frequency is applied to the system it will begin to oscillate at its maximum amplitude. This phenomenon is known as *resonance*.

This can be demonstrated when pushing someone on a playground swing, where the swing acts as a pendulum. Pushing the swing at its natural frequency makes the swing go higher and higher (maximum amplitude), while trying to push the swing faster or slower produces smaller arcs. This occurs because the energy the swing absorbs is maximised when the pushes match the swing's natural oscillations.

If the natural frequency of an intra-arterial blood pressure measuring system lies close to any of the frequencies of the sine wave components of the arterial pulse pressure waveform, then the system will resonate, producing excessive amplification and signal distortion (amplitude distortion).

The figure below demonstrates that at lower frequencies there is minimal amplitude distortion, however at higher frequencies, where the transduced signal approaches the resonant frequency of the system, significant distortion occurs.

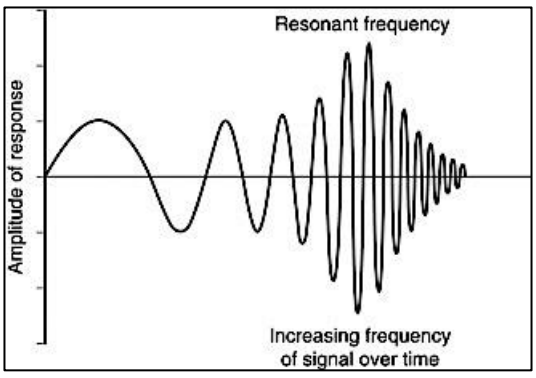


Fig 4: Amplitude distortion at increasing frequency

It is thus imperative that all the components of an intra-arterial monitoring system have a very high natural frequency – at least 8 – 10 times higher than the fundamental frequency of the arterial waveform (the pulse rate). So for the system to remain accurate for heart rates up to 180bpm, the natural frequency must be at least $\frac{180\text{bpm} \times 10}{60\text{sec}}$ = 30 Hz.

For a fluid filled system the resonant frequency (f_0) can be calculated with the following equation:

$$f_0 = \frac{1}{2\pi}\sqrt{\frac{\pi r^2}{p\ell}\frac{\Delta P}{\Delta V}}$$

r = the radius of the tubing
p = the density of the fluid
ℓ = the length of the tubing
$\frac{\Delta P}{\Delta V}$ = the elastance of the system

Thus, to obtain the highest possible natural frequency in an intra-arterial blood pressure monitoring system, we require shorter, wider, stiffer cannulae and tubing, with lower density fluid.

Damping

In practice the monitoring systems used do not posses a high natural frequency, and *damping* is introduced to decrease or eliminate amplitude distortion. Damping reduces the energy in the system (by creating friction in the fluid pathway) and thus reduces the amplitude of the oscillations. Some degree of damping is required in all systems, but if excessive (overdamping) or insufficient (underdamping), can be a major source of error.

Overdamping can be caused by:
- three way taps
- bubbles and clots
- vasospasm
- narrow, long or compliant tubing
- kinks in the cannula or tubing

Overdamping will result in an under-reading of systolic blood pressure and an over-reading of diastolic blood pressure. The response time of the system is also increased.

In an *underdamped* system pressure waves overshoot, with excessively high systolic blood pressures and low diastolic blood pressures.

Critical damping is the amount of damping required to prevent any overshoot. The damping co-efficient in a critically damped system is 1. However, this results in a system that is relatively slow to respond. A damping co-efficient of 0.64 (termed *optimal damping*) provides the best compromise between responsiveness and distortion.

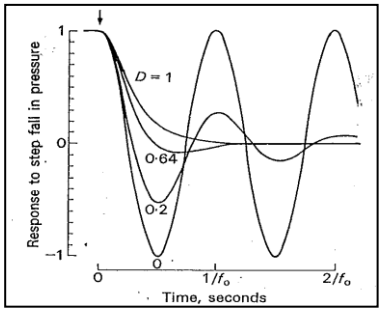


Fig 5: Damping co-efficient (D) – demonstrating the response to a step change in pressure

With a damping co-efficient of 0.64, amplitude is accurately replicated up to 2/3 of the natural frequency (within 2%), and only displays a maximal amplitude distortion of 6% at natural frequency.

In the clinical setting the damping co-efficient of a system can be calculated by using the *"fast flush" test* (see Fig 6 below). The monitoring system is flushed with high-pressure saline via a flush system, creating oscillating waves, resonating at the natural frequency of the system. The trace obtained is then printed and the amplitude of two successive waves measured, allowing the calculation of the

amplitude ratio ($^{A2}/_{A1}$). The amplitude ratio is converted to the corresponding damping co-efficient by using available conversion tables. Generally, a lower ratio corresponds to a higher damping co-efficient and a higher ratio represents a lower damping co-efficient.

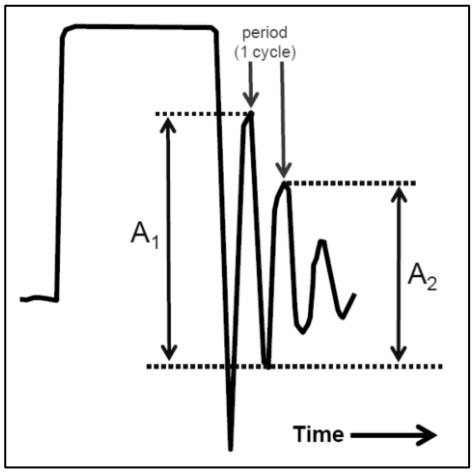


Fig 6: "Fast-flush" test

The fast-flush test is also used to determine the natural frequency of the system. The distance between the peaks of 2 successive waves (one cycle length) is measured and applied to the following formula:

natural frequency = $\frac{paper\ speed\ in\ mm/sec}{length\ of\ one\ cycle\ in\ mm}$

Therefore, in summary: damping is introduced into monitoring systems with low natural frequencies to decrease or eliminate amplitude distortion due to resonance.

Phase shift

As discussed before, the complex arterial pulse pressure waveform can be deconstructed into the fundamental wave with at least 10 additional harmonics. When these waves are summated by a microprocessor, not only their amplitude, but also their phase relationship will affect the displayed waveform. When no damping is present in a system, harmonic waves equal to the natural frequency of the system will be delayed by 90°, whilst those with a very low frequency will demonstrate almost no delay. Waves between these two extremes will demonstrate a variable amount of *phase lag*.

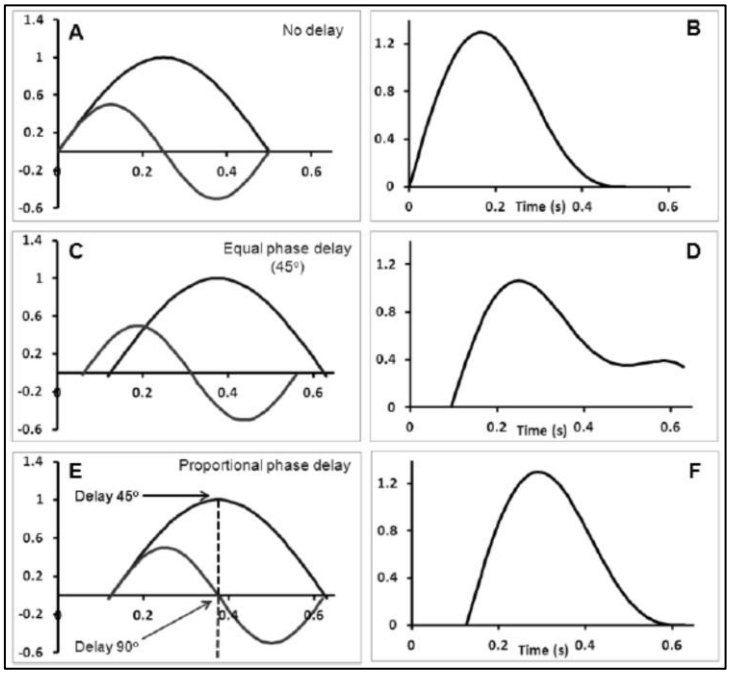


Fig 7: Phase shift – effect of equal versus proportional phase delay

To correct this phase lag, all harmonics need to be delayed in a linear proportion to their frequency. Harmonics with a frequency of 1f (the fundamental frequency) will need to be delayed by 90°, 2f by 180°, 4f by 360°, etc. This produces a delay in the displayed result, but allows the phase relationship of all waves to be preserved

Fortuitously, optimal damping (damping co-efficient = 0.64) provides precisely this proportional delay and allows the accurate summation of all harmonics.

Transducers

In the intra-arterial blood pressure measuring system the arterial pulse pressure is transmitted to a flexible diaphragm by a column of fluid – displacing the diaphragm. The commonest method of measuring this displacement is with a *strain gauge*. Strain gauges utilise the principle that the electrical resistance of wire or silicone increases with stretch. The flexible diaphragm is attached to wire or silicone strain gauges and then incorporated into a *Wheatstone bridge* circuit (see Fig 8 below). With movement of the diaphragm the gauges are stretched or compressed, altering their resistance.

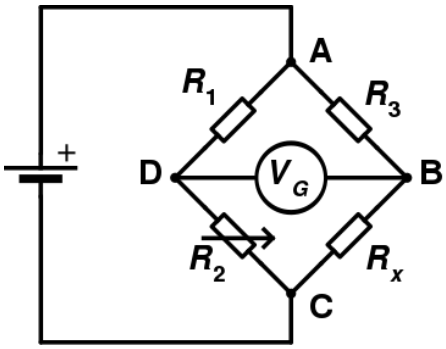


Fig 8: The Wheatstone bridge circuit. When R2/R1 = Rx/R3, the circuit is balanced and no deflection is registered on V_G

These circuits are constructed with 3 resistors of known resistance (R_1, R_2 and R_3) and one of unknown resistance (R_X). The resistance of R_2 is variable and can be adjusted to match the resistance in R_X, until the galvanometer (V_G) produces a zero deflection (voltage between B and D is zero). When pressure is applied to the diaphragm in the measuring system, the two sides of the bridge become unbalanced and current flows. The resistance in R_2 is then altered to maintain a zero balance between B and D, and the magnitude of this change in resistance is proportional to the pressure applied.

Modern Wheatstone bridge circuits have strain gauges in all four positions. The diaphragm is attached in such a way that when pressure is applied to it, the gauges on one side are compressed (reducing their resistance) and those on the other side are stretched (increasing their resistance). The bridge becomes unbalanced and the potential difference generated is proportional to the pressure applied. Using four strain gauges has 2 major benefits: (i) the system is four times more sensitive than a single strain gauge system and (ii) as a change in temperature can affect strain gauges, any temperature change in this system affects all of the strain gauges equally (in a single strain gauge setup temperature change can skew readings).

Zeroing and levelling

Zeroing
Atmospheric pressure must be discounted from the pressure measurement, for the pressure transducer to read accurately. This is achieved by exposing the transducer to atmospheric pressure and then calibrating the pressure reading to zero. As transducers are prone to baseline drift, this should be performed several times a day.

Levelling
The pressure transducer must be set at the level of the patient's heart, to measure blood pressure correctly. By convention this is set at the level of the right atrium, at the 4^{th} intercostal space in the mid-axillary line. If the transducer is placed above or below this level, the hydrostatic pressure exerted by the column of fluid (in this case blood) is being measured in addition to the blood pressure. For a 10cm error in levelling, the measured blood pressure will be over- or under-read by 7.4 mm Hg (over-read if the transducer is too low, under-read if too high).

Summary

The measurement of invasive blood pressure is one of the most valuable clinical tools in the management of critically ill patients. The underlying physical principles may be complex, but are essential to master – allowing the accurate interpretation of displayed values, and the identification of possible sources of error (resonance, damping, phase-shift, etc.)

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06

Inotropes

Dr Frank Schneider

Dept of Anaesthesia & Perioperative Medicine
University of Cape Town

An inotrope (derived from the Greek for turning or moving fibre), is the general term used to describe a substance which alters cardiac muscle contractility. Although inotropes can be positive or negative in their effect, this chapter will be limited to the discussion of positive inotropes and concentrate on their cardiovascular effect. A short review of definitions and basic pharmacology will hopefully help with understanding of mechanisms at a cellular level.

Definitions

Positive inotropes increase the force of contraction, but often also the rate of contraction or heart rate (**chronotropy**), ease of excitability of cardiac muscle (**bathmotropy**), velocity of conduction through cardiac tissue (**dromotropy**), and the rate of myocardial relaxation in diastole (**lusitropy**).

Sympathomimetics are substances that stimulate the sympathetic nervous system, and those found endogenously in humans are catecholamines, which act as both neurotransmitters and hormones. Other commonly used substances, such as ephedrine and phenylephrine, are not catecholamines but still have a sympathomimetic effect.

Catecholamines consist of a *catechol* (originally distilled from the plant extract *catechin*), which is a benzene ring with hydroxyl groups at the 3 and 4 positions, and an intermediate ethyl chain with a terminal amine. The length and composition of the side chain largely determine the properties and receptor affinity of the compound.

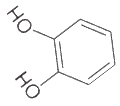


Figure 1
Benzene-3,4-diol

Naturally occurring endogenous catecholamines include dopamine, adrenaline (epinephrine) and noradrenaline (norepinephrine). The British Approved Name (BAN) for adrenaline and noradrenaline are in common use locally, but the International Nonproprietary Name (INN) epinephrine and norepinephrine are also used interchangeably in this chapter.

Dobutamine, isoprenaline and dopexamine are examples of synthetic catecholamines in clinical use.

Endogenous catecholamines are synthesised from the amino acid tyrosine (some of which is derived from phenylalanine), to form L-Dihydroxyphenylalanine (L-

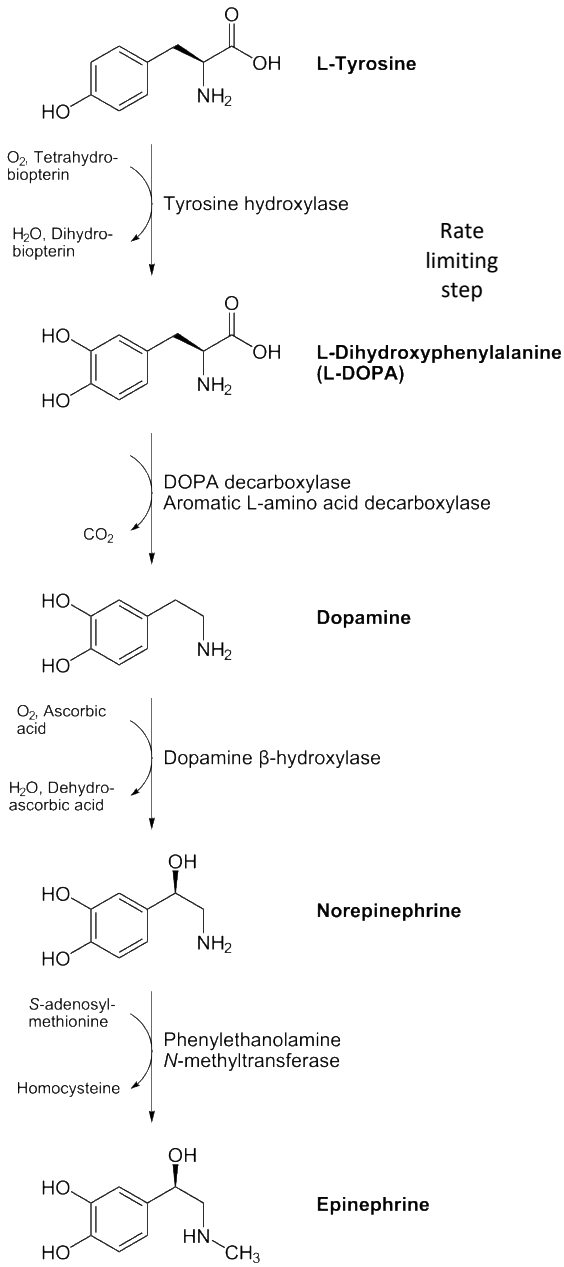


Figure 2 Biosynthetic pathway of endogenous catecholamines.

DOPA), in a rate-limiting step. L-DOPA is then converted further to dopamine, norepinephrine and epinephrine, which act at dopaminergic and adrenergic receptors respectively.
Dopamine has mostly paracrine and endocrine functions, suppressing the central release of thyroid stimulating hormone (TSH) and prolactin, acting on dopamine receptors in the chemoemetic trigger zone (CETZ) as well as regulating vascular tone in renal and other specialist vascular beds.
Noradrenaline is the neurotransmitter involved in signalling at almost all sympathetic nerve terminal synapses. The long postganglionic sympathetic neurons have varicosities along the terminal branches, filled with synaptic vesicles that synthesise and release noradrenaline. When an action potential reaches the terminal synapse, voltage-gated calcium channels are opened, rapidly increasing local intracellular calcium concentrations, which leads to fusion of the vesicle with the cell wall and exocytosis of noradrenaline in to the synaptic cleft.
Noradrenaline release also creates an autoinhibitory feedback mechanism via pre-synaptic α_2 receptors (fig. 3).
Adrenaline is predominantly synthesised and stored in the chromaffin cells of the adrenal medulla, and it functions as a hormone acting on distal targets following activation of the sympathetic nervous system. It is the main regulator of the "flight or fight" response.

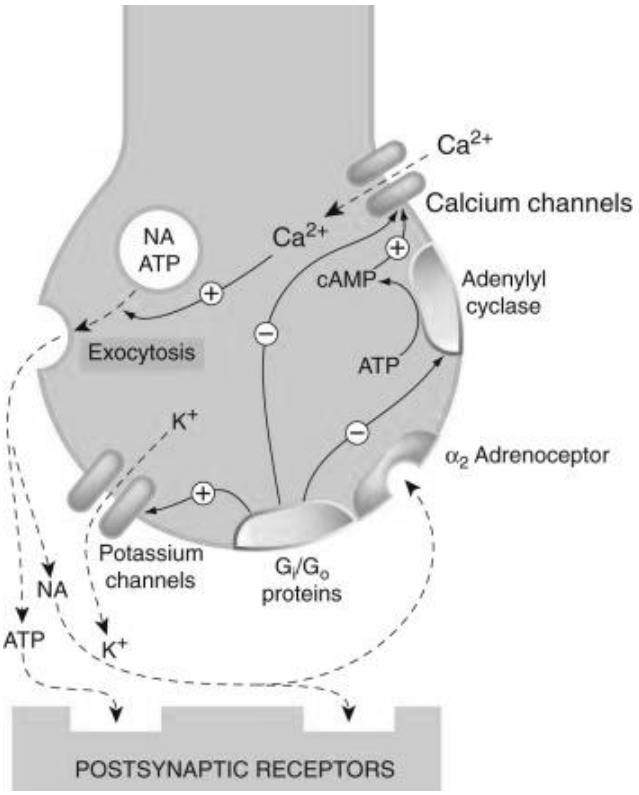


Figure 3 - Noradrenaline (NA) release and feedback control via inhibitory presynaptic α_2 receptors. Rang & Dale's Pharmacology 8Ed, Elsevier 2016

Receptors

Catecholamines act via cell membrane G protein-coupled receptors in various tissues, of which there are three β-adrenoceptor subtypes (β_1, β_2, β_3) and two main α-adrenoceptor subtypes (α_1, α_2), which are further differentiated in to three subclasses (α_{1A}, α_{1B}, α_{1D} and α_{2A}, α_{2B}, α_{2C}). There are at least five subtypes of dopamine receptors, but these are more easily considered as D_1-like or D_2-like.
When a catecholamine binds to the peptide chain of the receptor, a conformational change in the G protein initiates the production of a second messenger: inositol triphosphate (IP_3) in α_1, and cyclic adenosine monophosphate (cAMP) in β receptors. This ultimately leads to an increase in intracellular calcium and subsequent effect determined by the cell type. The exception is the inhibitory α_2 G protein, where stimulation causes a drop in cAMP and intracellular calcium levels.

> **α_1 receptors** are found in high concentration in vascular smooth muscle and activation in arterioles causes an increase in peripheral vascular resistance, whereas in the venous system, activation decreases venous capacitance, and increases venous return and cardiac preload. They also mediate direct vasoconstriction of pulmonary arteries and are found in low density in cardiac ventricular muscle, where they have some inotropic effect.

α_2 receptors form a complex arrangement of mostly "negative feedback" mechanisms, which attenuate the sympathetic response and generally cause a lowering of blood pressure.

β_1 receptors are concentrated in atrial and ventricular cardiac muscle, where stimulation results in positive inotropy, chronotropy, and lusitropy. Although this increases cardiac performance and output, it comes at the cost of increased myocardial work and oxygen demand.

β_2 receptors in the heart are found mostly in the atria, where stimulation predominantly causes an increased chronotropic effect, with a lesser inotropic effect due to the decreased receptor density on the ventricles. Receptors in skeletal muscle arteriolar beds cause vasodilatation and improved muscular blood flow upon stimulation, with an accompanying drop in peripheral vascular resistance. In non-cardiovascular clinical application, they are targeted for the treatment of bronchospasm (bronchial smooth muscle relaxation) and premature labour (uterine muscle).

β_3 receptors enhance lipolysis and thermogenesis when stimulated and are involved in negative feedback mechanisms that are less well understood. Stimulation may oppose β_1 effects, with a decrease in inotropy.

D_1 receptors in the periphery are found in the renal vascular bed and regulate vasodilation. Centrally they are involved in extrapyramidal activity. **D_2 receptors** inhibit further noradrenaline release peripherally, and reduce pituitary hormone output centrally.

Receptor Subtype		Location	Action when stimulated	Mechanism
α	1	Vascular smooth muscle	Vasoconstriction	G_q-coupled phospholipase C activated $\rightarrow \uparrow$IP3$\rightarrow \uparrow Ca^{2+}$
	2	Throughout nervous system	Sedation, analgesia, attenuation of sympathetic response	G_i-coupled adenylate cyclase inhibited $\rightarrow \downarrow$cAMP
β	1	Heart Platelets	+ inotropy/chronotropy Platelet aggregation	G_s-coupled adenylate cyclase activated $\rightarrow \uparrow$cAMP
	2	Vascular smooth muscle, bronchi, uterus Heart	Smooth muscle relaxation + chronotropy	G_s-coupled adenylate cyclase activated $\rightarrow \uparrow$cAMP
	3	Adipose tissue	lipolysis	G_s-coupled adenylate cyclase activated $\rightarrow \uparrow$cAMP
D	1	Peripherally CNS	Vasodilatation of renal and mesenteric Extrapyramidal activity	G_s-coupled adenylate cyclase activated $\rightarrow \uparrow$cAMP
	2	Peripherally CNS	Inhibit NA release $\downarrow$pituitary hormone output	G_i-coupled adenylate cyclase inhibited $\rightarrow \downarrow$cAMP

Table 1 Actions and mechanisms of adrenoceptors. IP3 = Inositol triphosphate, cAMP = cyclic adenosine monophosphate, NA = noradrenaline, CNS = central nervous system.

Naturally Occurring Inotropes

Dopamine acts both directly and indirectly. The absence of functional groups on the ethylamine sidechain allow it to enter sympathetic nerve terminals and displace noradrenaline from storage vesicles, causing an adrenergic effect, as long as noradrenaline stores have not been depleted.

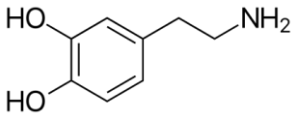


Figure 4 Dopamine

Direct function (at doses around 5 μg/kg/min) is via binding to dopamine receptors. Dopamine's structure does not give it great affinity for β and α receptors, but at doses up to 10-20 μg/kg/min, β_1 receptors may be stimulated, causing increased heart rate, contractility and cardiac output. At even higher doses (>20 μg/kg/min), α effects predominate, with peripheral vasoconstriction and increased systemic vascular resistance and venous return.

Dopamine has therefore been described as a general inotrope-vasopressor, but its wide and unpredictable dosage range, as well as reliance on indirect mechanism of action, usually make it a suboptimal choice of inotrope. In addition, it is a potent emetogenic, supresses prolactin release (impairing immunity) and TSH release.

The "renoprotective" benefit of dopamine has long since been convincingly disproven, despite its continued use in certain centres. Urine output in these patients had likely increased due to the diuretic effect of dopamine (inhibiting renal tubular reabsorption of sodium), rather than improved renal perfusion. If anything, dopamine causes maldistribution of blood flow from the renal medulla to the cortex, and may worsen renal outcomes.

Noradrenaline differs from dopamine by the addition of a single hydroxyl group on the ethylamine sidechain, making it a direct-acting drug with a high affinity for α receptors and moderate affinity for β_1 receptors, without much β_2 effect. This makes it a potent vasoconstrictor via α_1 agonism (and lack of β_2 vasodilatation) as well as a mild inotrope via a moderate β_1 effect. It is arguably the agent of choice in states of distributive shock, such as the systemic inflammatory response syndrome (SIRS) or sepsis. It is available in South Africa, but can be complicated to obtain for routine clinical use.

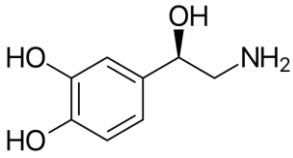


Figure 5 Noradrenaline

Adrenaline is formed from noradrenaline, with the addition of a methyl group on the terminal amine, greatly increasing affinity for both β_1 and β_2 receptors. At lower doses it acts predominantly as a β agonist and inotrope, with some vasopressor action. At higher doses (around 1μg/kg/min) the α_1 vasopressor activity dominates, but is not as potent as noradrenaline, due to the offset vasodilation via β_2 activity.

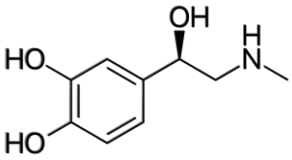


Figure 6 Adrenaline

Adrenaline is readily available and in common use globally. Its positive chronotropic and inotropic action causes increased cardiac workload, and together with additional arrhythmogenicity, it may put patients with ischaemic heart disease at risk. Plasma glucose is raised by stimulating glycogenolysis, lipolysis and gluconeogenesis, and may also be affected by changes in insulin secretion (increased by β_2, but overridden by α effects). Although it is a significant vasopressor, lactate rise is usually due to increased glycolytic flux rather than vasoconstriction and anaerobic metabolism.

Adrenaline is recommended at a dose of 1mg every 2-4 minutes, as part of the resuscitation guidelines in cardiac arrest, where it is hoped to function as a pure vasopressor and intended to direct blood supply to vital organs.

Pharmacokinetics, metabolism and administration. Endogenous catecholamines have short half-lives of around a minute, due to diffusion away from their sites of action, and efficient metabolism by one of two enzymatic pathways. Monoamine Oxidase (MAO) is present in high concentrations in nerve terminals, whereas Catechol-O-Methyl-Transferase (COMT) degradation occurs in the liver and kidneys. Both transformations usually occur, producing vanillylmandelic acid (VMA) from adrenaline and noradrenaline, and homovanillic acid from dopamine.
Due to the short half-life and efficient metabolism, adrenaline and noradrenaline are normally given by continuous infusion at a dose range of 0.01 – 0.5 μg/kg/min, and dopamine started around 1 – 5 μg/kg/min. Titration of doses should occur according to clinical effect, aiming to achieve a pre-determined target, for example, a mean arterial pressure (MAP) of around 60mmHg. Extravasation can cause tissue necrosis, so infusions are given via central venous catheters in all but emergency situations. Adrenaline doses above 1 μg/kg/min are unlikely to produce additional benefit, as all receptors are maximally occupied. Adequacy of circulating cortisol levels, desensitisation and downregulation of receptors may be more important factors in these poor responders.

Synthetic Inotropes
Of the synthetically produced agents, only isoprenaline, dobutamine and dopexamine are classified as catecholamines.

Isoprenaline is now rarely found to be in clinical use, due to manufacturing issues. It is a pure β agonist and was favoured for its chronotropy (useful in chemical pacing of bradycardias and denervated hearts) and inotrope-vasodilator action (useful postoperatively in paediatric cardiac patients unable to tolerate increased afterload).

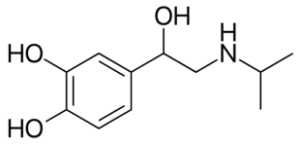


Figure 7 Isoprenaline

Dobutamine resembles dopamine but has a large hydrocarbon tail which ensure it is direct-acting and increases β receptor selectivity. It was designed to be a pure β agonist and has been termed an "inodilator" due to the inotropic effect at β_1 receptors, combined with the afterload-reducing vasodilatory effect of β_2 receptor stimulation in the skeletal muscle vascular beds. It also increases atrioventricular conduction and may precipitate arrhythmias, or increase the ventricular response rate in patients with atrial fibrillation or flutter.

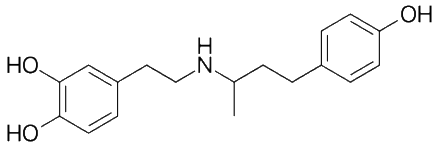


Figure 8 Dobutamine

It is used in the treatment of low cardiac output states in heart failure and cardiac surgery, at a dose range of 1 – 20 μg/kg/min. It can also be used for cardiac stress testing as an alternative to exercise.

Dopexamine is structurally similar to dopamine and dobutamine, with potent β_2 agonism and minimal β_1 effects, as well as potent D_1 agonism with minimal D_2 and no α_1 action. It causes positive inotropic effects due to cardiac β_2 stimulation, which together with reduced regional vascular resistance, increases splanchnic blood flow. It is now seldom used clinically.

Phenylephrine is not a catecholamine, due to the loss of a hydroxyl group from the benzene ring, but otherwise looks identical to adrenaline. This relatively minor structural change prevents it binding at β receptors, and it is a pure α agonist, causing an increase in systemic vascular resistance and blood pressure. It is far less potent than adrenaline, and must be given in 10-fold higher doses (50 – 100μg boluses intravenously). Degradation by COMT is also less effective, meaning the duration of action is longer. It should be used with caution, or not at all, in the setting of relative bradycardia or decreased inotropic states, where a β agonist should be considered in order to avoid precipitating acute cardiac failure.

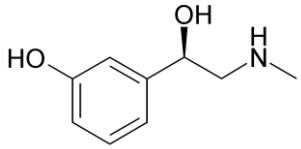


Figure 9 Phenylephrine

Ephedrine is a naturally occurring stimulant in *Ephedra* plants, but is manufactured synthetically for clinical use. The absence of hydroxyl groups means that it is lipid soluble enough to enter neurons and act indirectly by releasing noradrenaline, its major mechanism of action. It is far less potent as a direct agonist and 1000-fold doses are required, also leading to rapid depletion of stored noradrenaline. It is not degraded by MAO or COMT and therefore has a longer duration of action.
Ephedrine causes a mild increase in inotropy and vasoconstriction when given in intravenous boluses of 5 – 10mg. It may become ineffective after repeated doses or in patients in whom noradrenaline stores are depleted.

Amphetamines also have a benzene ring with no hydroxyl group, are highly lipid soluble and penetrate the blood-brain-barrier with ease. Although they have no direct adrenoreceptor effect, they displace catecholamines from neuronal storage vesicles and can cause central release of large amounts of catecholamines. Originally developed as medication for appetite suppression and mood disorder, they have subsequently mostly become drugs of abuse.

Phosphodiesterase (PDE) inhibitors are positive inotropes that are not dependant on adrenoceptor activation, as they increase the intracellular action of cAMP and cyclic guanosine monophosphate (cGMP) by preventing their degradation. This may be particular useful in cardiac failure when downregulation of β receptors has occurred. The selective PDE III inhibitor milrinone allows accumulation of cAMP in the cardiac myocyte, increasing cardiac contractility, enhancing left ventricular relaxation and improving early ventricular filling. Conversely, in smooth muscle, ↑cAMP prevents calcium release and promotes smooth muscle relaxation and reduced peripheral and pulmonary vascular resistance.

Digoxin causes a modest increase in contractility by reversibly binding to Na^+-K^+-ATPase in the cardiac myocyte, which leads to increased availability of intracellular calcium and increased contractility.

Levosimendan is a myocardial calcium sensitiser and inodilator, which improves contractility without increasing intracellular calcium or cAMP, and thereby doesn't increase myocardial oxygen demand.

	Receptors Stimulated			Cardiac Effects									
	α	β_1	β_2	Mechanism of Action	Cardiac Output	Heart Rate	Dysrhythmias	Peripheral Vascular Resistance	Renal Blood Flow	Mean Arterial Pressure	Airway Resistance	Central Nervous System Stimulation	Single Intravenous Dose (70-kg Adult)	Continuous Infusion Dose (70-kg Adult)
Natural catecholamines														
Epinephrine	+	++	++	Direct	++	++	+++	±	−−	+	−−	Yes	2–8 μg	1–20 μg/min
Norepinephrine	+++	++	+	Direct	−	−	+	+++	−−−	+++	NC	No	Not used	4–16 μg/min
Dopamine	++	++	+	Direct	+++	+	+	+	+++	+	NC	No	Not Used	2–20 μg/kg/min
Synthetic catecholamines														
Isoproterenol	0	+++	+++	Direct	+++	+++	+++	−−	−	±	−−−	Yes	1–4 μg	1–5 μg/min
Dobutamine	0	+++	+	Direct	+++	+	±	NC	++	+	NC		Not used	2–10 μg/kg/min
Synthetic noncatecholamines														
Ephedrine	++	+	+	Direct and indirect	++	++	++	+	−−	++	−−	Yes	10–25 μg	Not used
Phenylephrine	+++	0	+	Direct	−	−	NC	+++	−−−	+++	NC	No	50–100 μg	20–50 μg/min

0, none; +, minimal increase; ++, moderate increase; +++, marked increase; −, minimal decrease; −−, moderate decrease; −−−, marked decrease; NC, no change.

Table 2 - Classification and Comparative Pharmacology of Sympathomimetics. From *Stoelting's Pharmacology and Physiology in Anesthetic Practice, 5 Ed, Wolters Kluwer 2015*

Notes

Temporary Pacemakers

Dr Owen Porrill

Private Practice
Honorary lecturer- University of Cape Town

Temporary pacemakers are usually inserted as part of the urgent management of severe arrhythmias, usually bradyarrhythmias. They may also be inserted for prophylactic indications e.g. patients with a high-grade AV block undergoing surgery. Rapid atrial pacing is also used to decrease cardiac output e.g. during TAVI placement. The sites of insertion we are most likely to encounter as anaesthetists are transvenous or epicardial after cardiac surgery. Other routes of pacing are transcutaneous or oesophageal, which require different equipment and will not be discussed in detail in this course.

Temporary pacemakers consist of a pulse generator (box) and insulated wires, also known as leads. The box contains the controlling circuitry and a battery and has two basic functions. The first is to sense electrical activity in one or more cardiac chambers. The other is to pace the atrium, ventricle or both.

Leads:

Leads may be transvenous/endocardial or epicardial/myocardial. Endocardial leads are introduced via the venous system and are placed in contact with the endocardium. Epicardial leads are applied to the external surface of the heart and are introduced through the chest wall during cardiac surgery (atrial on the right, ventricular on the left). Epicardial leads are usually sutured in place.

Transvenous leads aremade of a metal alloy insulated by polyurethane or silicone. They may be flexible, semifloating (with or without a balloon tip) or rigid. They may also be incorporated into a pulmonary artery catheter. Rigid wires are inserted under fluoroscopic guidance, the others are inserted blindly or under ECG guidance. The best insertion sites are the left subclavian or right internal jugular veins, due to the curvature of the lead. The femoral vein may occasionally be chosen in anticoagulated patients. The side of the dominant hand is often used as a permanent pacemaker may subsequently be placed on the non-dominant side. Ultrasound may be very useful in placement of the leads, both for vascular access and to visualise the lead in the cardiac chambers and to see ventricular contraction in response to stimulation. Ultrasound may also be useful in diagnosing complications of the procedure e.g. haemopericardium or pneumothorax.

Fixation of endocardial leads may be passive or active. Passive fixation occurs by means of fins or tines (small prongs) which become enmeshed in the trabeculae of the ventricular apex or the pectinate muscles of the atrium. Active fixation occurs by means of hooks, barbs or screws into the myocardium. Active fixation decreases the chance of losing contact with the myocardium, but does increase the risk of myocardial perforation, particularly in older patients.

The pulse generator, leads and body tissue are all components of the electrical circuit. Most leads nowadays are bipolar, meaning that the positive and negative electrodes are contained within the lead. The current flows from the pulse generator to the tip of the pacing lead (cathode). The anode is a metallic ring a few millimetres from the tip. In unipolar leads the current flows from the pulse generator to the cathode and back to the box which acts as the anode. Unipolar leads require a higher current due to the increased impedance. Unipolar leads are also more sensitive to electromagnetic interference and have a higher risk of diaphragmatic or chest wall muscle pacing. Unipolar leads usually cause a larger pacing spike on the surface ECG.

Tripolar or quadripolar leads are used to pace the left ventricle during cardiac resynchronisation therapy. This is used in patients with a low ejection fraction and a widened QRS complex. The lead is usually placed into a vein on the left ventricular epicardium via the coronary sinus. The presence of 3 or 4 electrodes allows avoidance of scarred myocardium and decreases the incidence of phrenic nerve pacing.

Leads may be inserted into the atrium, ventricle or both, depending on the indication for pacing.

External Pacing Generator:

This will have the following controls and capabilities:

1) Rate: Controls heart rate
2) Output: This controls the output current in milliamperes, usually between 0,1 and 20 mA
3) Sensitivity: Senses native electrical activity in the cardiac chamber. The sensitivity control sets a threshold at which pacing will be inhibited.

Rate:

In practice, the rate is usually set at 80-90 per minute. The rate is sometimes reduced to 40 before pacemaker removal as a backup rate.

Sensing:

The pacemaker senses intrinsic cardiac activity. This is measured in millivolts. The sensing threshold can be adjusted by the user. Remember that increasing sensitivity means decreasing the threshold in mV and vice versa (detection of smaller potential difference equals higher sensitivity). The sensing threshold must be checked if the pacemaker is to be used in demand or synchronous mode. The pacemaker should be in VVI, AAI or DDD mode. Set the pacing rate 10 beats per minute less than the intrinsic rate and the output at 0,1 mA. Set the sensitivity at its highest (demand mode). The pacemaker should only sense and not pace. Decrease the sensitivity until the pacer starts pacing and the sensing indicator stops flashing. Increase the sensitivity until the sense indicator starts flashing and the pace indicator stops flashing. This is the pacing threshold. Set the sensitivity at half of the threshold value for a margin of safety, but to avoid undersensing. If there is no underlying rhythm, set the sensitivity at 2 mV.

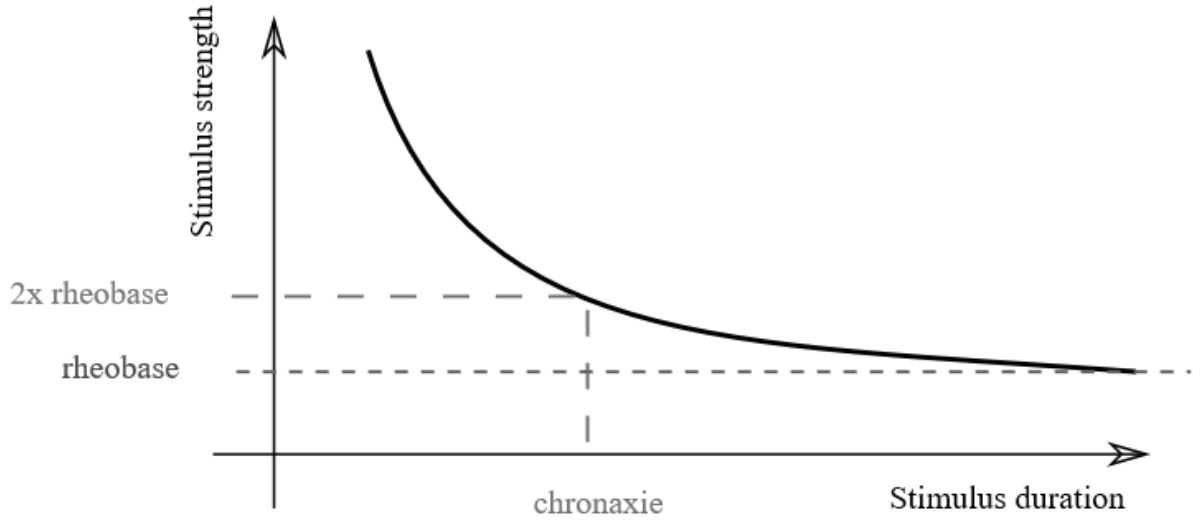
The pacemaker interprets any activity as either a P or R wave. Sensing filters exclude myopotentials, T waves, pacemaker activity on a different channel (crosstalk) and other extraneous signals (oversensing).

The asynchronous mode is potentially dangerous and should only be used in a highly monitored environment. We often use the asynchronous mode in theatre to avoid oversensing due to electromagnetic interference. If the pacemaker delivers a stimulus during ventricular repolarisation (R-on-T phenomenon), ventricular fibrillation may be precipitated. The pacemaker should always be reprogrammed to a synchronous mode before the patient moves to a general ward.

Physiology of pacing:

An electrical stimulus will cause depolarisation and subsequent action potential propagation if the energy delivered exceeds a certain threshold. The energy delivered is a function of current delivered and the time over which the current flows. Each excitable tissue has its own threshold. The current is usually negative to decrease membrane potential and initiate an action potential.

The energy required is described by the strength duration curve. Electrical capture will occur in the area to the right of the curve. The rheobase is the minimum current required to elicit a response if the stimulus duration is very long. The chronaxie is the time required to elicit a response at a current twice the rheobase. These are not terms you will use on a day-to-day basis, but they are important to electrophysiologists and engineers designing equipment such as pacemakers and nerve stimulators. Practically, a pacemaker generates a continuous current for about 1,5 milliseconds, which approximates the chronaxie of cardiac muscle. The time is not adjustable, but the user can control the current output.



To set the appropriate output, you need to determine the pacing threshold. It is unsafe to check the threshold in the absence of an underlying rhythm as you may not be able to re-establish capture. If it is safe to check the threshold, set the pacing rate at 60-80 beats per minute, or at least 10 beats per minute faster than the patient's intrinsic rate. Start with a high current output and decrease the current until capture is lost. Increase the current until consistent capture is demonstrated (each pacing spike is followed by a p wave or QRS complex). This is the threshold value. The output is then set to 2-3 times this value to ensure reliable function. If it is >10 mA, a smaller margin of safety is used to avoid accelerating myocardial fibrosis. The threshold should be checked regularly as it can rise over time as an inflammatory reaction develops around the lead implantation site. Pacing threshold also changes during the day(increased during sleep) and with certain drugs. Temporary endocardial wires may be steroid eluting to decrease the inflammatory response and are generally reliable for periods of up to two weeks. Epicardial pacing wires have a shorter lifespan, often failing to pace and/or sense by day 5. This is known as an exit block. Unnecessarily high pacing output will decrease the life span of the temporary lead and increase the inflammatory response in the myocardium. Permanent pacing wires are steroid eluting (usually dexamethasone).

To reassess the underlying rhythm, it is important to turn down the pacing rate and allow the native rhythm to manifest. If the current is decreased to allow the underlying rhythm to emerge, the threshold for recapture may be dramatically increased and it may be impossible to resume pacing (Wodinsky effect). The underlying rhythm should always be assessed and must be more than 50 per minute and the patient must remain haemodynamically stable before sensitivity and capture thresholds are assessed (in that order).

Pacemaker modes:

The NBG code for pacemakers applies to temporary pacemakers. The first 3 positions are the most relevant, but biatrial or biventricular pacing is occasionally used after cardiac surgery.

The revised NASPE/BPEG generic code for antibradycardia pacing

I	II	III	IV	V
Chamber(s) paced	Chamber(s) sensed	Response to sensing	Rate modulation	Multisite pacing
O = None	O = None	O = None	O = None	O = None
A = Atrium	A = Atrium	T = Triggered	R = Rate modulation	A = Atrium
V = Ventricle	V = Ventricle	I = Inhibited		V = Ventricle
D = Dual (A+V)	D = Dual (A+V)	D = Dual (T+I)		D = Dual (A+V)

Common modes used are AAI, VVI, DDD, DOO and AOO, depending on the scenario. The asynchronous modes (AOO, DOO, VOO) are generally only used in theatre when diathermy is used or during an emergency when there is malfunction of one of the more advanced modes. Atrial pacing is used for bradycardias with intact ventricular conduction. DDD is the most useful mode as it preserves AV synchrony. VVI has the advantage of simplicity, requiring only 1 lead to be inserted. VDD is occasionally used in cases of AV nodal block with an intact sinus node. Triggered modes (VAT, AAT, DAT) are not commonly used in temporary pacing.

Atrial overdrive pacing may be used for supraventricular tachycardias, but that will not be discussed in detail here.

Typical settings for postoperative patients:

Rate: 80-90 bpm

Output: 10mA (atrium) 10-20 mA (ventricle)

Sensitivity: 5 mV (atrial 0,4-10 mV, ventricle 0,8-20 mV)

AV delay: 150 ms (or auto depending on rate). May be changed to optimise cardiac output

PVARP: 250 ms (or auto depending on rate)

Complications:

Complications of temporary pacing include complications of central venous cannulation as well as complications related to the pacemaker. These include mechanical complications such as perforation of the heart or ventricular septum, infection, looping, damage to the tricuspid valve, misplacement or interference with vascular anastomoses. There may also be problems of functionality e.g. failure to sense or capture.

Failure to capture is recognised when pacing spikes are seen, with no cardiac activity. This is usually caused by lead failure, but other causes may be hypoxia, ischaemia, acidosis, alkalosis, electrolyte abnormalities (particularly hyperkalaemia) and antiarrhythmic drugs. A temporary solution in an emergency is to reverse the polarity of the electrodes. If a bipolar lead is used, the anode can be used as the cathode and a return electrode inserted subcutaneously.

Failure to sense has similar causes to failure to capture.

Crosstalk can occur with dual chamber pacemakers, with pacing of one chamber inhibiting the pacing of the other chamber. This most commonly manifests as atrial pacing misinterpreted as ventricular activity, resulting in ventricular standstill. This can usually be addressed by increasing the ventricular sensitivity and/or decreasing the atrial output. Modern pacemakers have two safety features to prevent ventricular standstill. Ventricular blanking ensures that ventricular activity is ignored for a short period after atrial depolarisation. If the pacemaker detects ventricular activity after the ventricular blanking period but before it would expect with normal AV conduction (i.e. during the cross-talk sensing window), it assumes there is either cross-talk or a PVC. It then emits a ventricular spike slightly early after the next atrial depolarisation (i.e. it decreases the AV delay of the next cycle) to avoid ventricular standstill. This is known as ventricular safety pacing.

Pacemaker mediated tachycardia can occur in DDD or VDD modes and has various causes. It most commonly occurs when there is atrial sensing of a ventricular spike. This is interpreted as atrial depolarisation and triggers ventricular pacing and subsequent tachycardia. The pacemaker employs an atrial blanking period to prevent this, during which it will not sense any ventricular depolarisation. It may also occur due to retrograde p waves via an accessory pathway setting up a re-entrant circuit. PVARP (post ventricular atrial refractory period) can be manually prolonged on the pacemaker in this scenario to prevent ventricular pacing in response to the retrograde p wave. Changing to VVI or DVI mode temporarily should also terminate the tachycardia, but this should only be employed temporarily while a definitive solution is found.

Tachycardia can also occur due to inappropriate tracking of a high atrial rate. Modern pacemakers will usually set the upper rate automatically. When the rate reaches this limit, the pacemaker introduces an artificial Wenkebach phenomenon, increasing the AV delay until the atrial spike falls within the PVARP and the impulse is ignored. When this occurs, the tachycardia should be treated or the mode changed to DDI.

Microshock is a danger as these leads are connected directly to the heart. All power sources should be ungrounded and any sources of static should be removed (including Get Well Soon balloons!). Gloves should be used when handling the wires. Anyone handling the wires should touch a large metal object (e.g. the bed) to discharge static build-up before handling the wires.

Removal of the leads can lead to *haemorrhage* and *arrhythmias*, thus patients should be appropriately monitored during and after removal.

Permanent Pacemakers

Many of the above principles apply to permanent pacemakers. Permanent pacemakers are more sophisticated and employ other features. The box is made of titanium and contains a battery (usually lithium iodide), a motherboard, sensors and pulse generator. It is usually implanted in a pre-pectoral location and the leads inserted via the cephalic or subclavian vein. The box has an X-ray identifier visible on chest X-ray and the patients are given a detailed card on insertion of the pacemaker.

Permanent pacemakers have a magnet operated reed switch, or reed relay. This was originally used to induce an asynchronous pacing mode, but this is not the case in all modern pacemakers. Response is unpredictable and magnet use is not recommended without consulting the manufacturer.

Rate modulation is present in many permanent pacemakers. The rate changes in response to a stimulus to improve the response to physiological stress. The sensor may be a movement sensor such as an accelerometer, or a physiological sensor such as minute volume, temperature sensor, QT interval or contractility. This should be deactivated before surgery.

Implantable cardioverter defibrillators

These are inserted for primary or secondary prevention of death from ventricular tachycardia or fibrillation. They consist of pacing and sensing electrodes, a battery, capacitor, pulse generator and a defibrillator (shock) coil (which is easily identifiable on X-ray). The box is usually larger than a pacemaker box. They measure R-R intervals to detect ventricular tachycardia and fibrillation. The therapeutic interventions are overdrive antitachycardia pacing (ATP), low energy cardioversion and high energy defibrillation. They generally also have antibradycardia pacing capability in case of post-shock bradycardias.

Table 3 NASPE/BPG Generic Defibrillator Code (NBD).[2]

Position I shock chambers	Position II antitachycardia pacing chambers	Position III tachycardia detection	Position IV antibradycardia pacing chambers
O = none A = atrium V = ventricle D = dual (A + V)	O = none A = atrium V = ventricle D = dual (A + V)	E = electrogram H = hemodynamic monitors	O = none A = atrium V = ventricle D = dual (A + V)

These should always be deactivated before surgery in case of oversensing due to electromagnetic interference in theatre. Most are deactivated by a magnet, but they should be deactivated by a technician if possible.

Clinical Considerations

These will be very briefly mentioned as discussion is more appropriate in a part 2 course.

Electromagnetic interference (EMI)

This is the major consideration in the operating theatre. Monopolar diathermy is the major source and can cause oversensing and inhibition of pacing. Bipolar diathermy is preferred if possible. Other sources are mobile phones and wireless devices e.g. ultrasound probes.

MRI

The presence of a pacemaker or ICD is a relative contraindication to MRI. If an MRI is necessary, a cardiologist should be consulted and a strict protocol followed.

Radiation therapy

This is usually safe, but direct radiation of the device should be avoided

Radiofrequency ablation

ICD's should be deactivated and the device should not be too close to the pacemaker/ICD and leads.

Extracorporeal shock wave lithotripsy (ESWL)

Generally safe, but the lithotripter should be kept 15cm away from the device. Rate modulation should be deactivated. The pulse should not be aimed at the device and should be timed with the ECG.

Electroconvulsive Therapy (ECT)

The defibrillator should be deactivated. Rate modulation should probably be deactivated and some patients may require reprogramming to an asynchronous mode.

Transcutaneous electrical nerve stimulation (TENS)

This should not be used in close proximity to the device

Electricity & Electrical Safety

Dr Dominique van Dyk

Dept of Anaesthesia & Perioperative Medicine
University of Cape Town

There are 4 ways in which electricity may cause harm to a patient or operating room staff:

1) Current flow through the body → electrical shock
2) Loss of electrical power → equipment failure
3) Interference with function of implanted devices, e.g. pacemakers or defibrillators
4) Thermal injury- fires, burns, explosions

These notes will focus on the prevention of electrocution of our surgical patients, operating room colleagues and us as anaesthetists!

South African legislation of relevance to electrical safety in operating rooms:

The Occupational Health and Safety Act, 1993 (Act No. 85 of 1993)-

- Refers to the Electrical Installation Regulations of 2009 and the Code of Practice for Wiring of Premises SANS 10142-1.
- Is managed by the Department of Labour
- Covers the use of products in electrical installations, generally applicable to products for fixed installations such as socket outlets, wall switches and circuit breakers.
- Prescribes the Wiring Code (SANS 10142-1) for the wiring of fixed installations in the work environment.

SANS 60601-1:2013 is the South African National Standard that delineates the "General requirements for basic safety and essential performance" of medical electrical equipment.

Basic concepts

Atoms, electrons, charge

Matter is composed of atoms. Atoms are composed of electrons (-) orbiting around a nucleus of protons (+) and neutrons.
Electric *charge* is the physical property of matter that causes it to experience a force when placed in an electromagnetic field.
Electrons have a negative charge. Protons have a positive charge. Opposite charges attract. Like charges repel.
An electric (force) field surrounds any charged object – it spreads out and weakens with distance.
Charge is measured in Coulombs. 1 Coulomb = the amount of charge transported by a current of 1 ampere in one second.
The charge of one electron is -1.6×10^{-19} Coulombs.
1 Coulomb $= \frac{1}{-1.6*10^{-19}} = 6.25*10^{18}$ electrons
The number of protons in an atom determines what the element is. For instance: Hydrogen- 1 proton and 1 electron; Aluminium- 13 protons and 13 electrons. Electrons orbiting the atomic nucleus are organized into shells. In the case of aluminium, its 13 electrons are organized into three shells: 2 electrons in the innermost shell, 8 electrons in the middle shell, and 3 electrons in the outermost shell. The 3 electrons in the outermost shell are the valence electrons.

Free electrons and current

When a valence electron in any atom gains sufficient energy from some outside force [e.g. friction (static), thermal (thermocouple), light (photocell), chemical (battery) or electromagnetic (generator)], it can break away from the parent atom and become what is called a **free electron**. Atoms with few electrons in their valence shell tend to have more free electrons since these valence electrons are more loosely bound to the nucleus. In some materials, like copper, the electrons are so loosely held by the atom, and are so close to the neighboring atoms, that it is difficult to determine which electron belongs to which atom. Under these conditions, the free electrons tend to drift randomly from one atom to its neighboring atoms. Under normal conditions the movement of the electrons is truly random, meaning they are moving in all directions by the same amount. However, if some outside force acts upon the material, this flow of electrons can be directed through materials and this flow is called **electrical current**.

So, the flow of free electrons through a conductor is called current. Current will only flow when a circuit with a voltage source is completed. ***If there is the choice of two paths in parallel to complete a circuit, the greater current will flow along the path with the lower resistance***.

Conductors and insulators

Materials that have free electrons and allow electrical current to flow easily are called **conductors**. Good electrical conductors are copper, aluminium, gold, silver, and platinum.

Many materials do not have any free electrons. Because of this fact, they do not tend to share their electrons very easily and do not make good conductors of electrical currents. These materials are called **insulators**. Insulators are used to isolate electrical components and prevent current flow. Good electrical insulators are rubber, porcelain, glass, and dry wood.

Insulator Characteristics:

1) Resistance- The ability of the insulator to resist current leakage through and over the surface of the insulator material.
2) Dielectric Strength- The ability to withstand a maximum voltage without breakdown damage to the insulator.

Ohm's Law: $V = I \times R$,

where V is the electromotive force (potential difference between two points) in Volts, I is the current in Amperes, and R is resistance in Ohms.

Electrical power formula: $W = V \times I$,

where W is the power in Watts, V is the electromotive force in Volts, and I is the current in Amperes. From Ohm's Law, $W = (I \times R) \times I = I^2R$. The *watt* (abbreviated W) is the SI standard unit of power (energy per unit time), the equivalent of one joule per second. Wattage can be considered not only as a measure of work done, but also of *heat produced* in an electrical circuit.

Direct vs alternating current:

Direct current (DC) is current that flows consistently in one direction, e.g. a torch powered by batteries. For DC, Ohm's Law holds true.

Alternating current (AC) is current in which the direction of electron flow switches back and forth at regular intervals or cycles, e.g. normal household electricity that comes from a wall outlet. A graph of Voltage vs Time resembles a sine wave. Advantages of AC: (1) relatively cheap to change the voltage of the current, (2) far less energy lost when current is carried over long distances as AC vs DC.

For AC, the "resistance" to current flow is more complex, and is called **impedance** (Z). **Impedance** is the sum of forces opposing electron movement in an AC circuit, which include resistance (R), inductance and capacitance. For AC, Ohm's Law is defined as $V = I \times Z$, and the current flow is inversely proportional to the impedance. The amount of current flowing through a given device is

frequently referred to as the *load. A* very high impedance circuit allows only a small current to flow and thus has a small load. A very low impedance circuit will draw a large current and is said to be a large load. A *short circuit* occurs when there is a zero impedance load with a very high current flow

Inductance is a property of current-carrying conductors whereby a change in current can result in generation of voltage (called electromotive force) in the conductor itself as well as a conductor placed in its vicinity. Inductance occurs because of fluctuations in the surrounding magnetic field and is described by **Faraday's law of inductance**.

Capacitance is the ability of a device to store electric charge. An electronic component that stores electric charge is called a capacitor. The simplest capacitor consists of two flat conducting plates separated by a small gap. The potential difference, or voltage, between the plates is proportional to the difference in the amount of the charge on the plates. This is expressed as Q = CV, where Q is charge, V is voltage and C is capacitance. The capacitance of a capacitor is the amount of charge it can store per unit of voltage. The unit for measuring capacitance is the farad (F), named for Faraday, and is defined as the capacity to store one coulomb of charge with an applied potential of one volt. **Alternating current can flow through a capacitor, whereas DC cannot.**

Generation of electricity

Almost all the electronic devices used by anaesthetists run on mains electricity, supplied by Eskom.

In the case of a coal-fired plant like Medupi, pulverized coal enters a furnace, to heat water circulating through pipes to make steam. High-pressure steam spins a turbine, which rotates a central shaft connected to a generator. The generator converts the mechanical energy of the spinning shaft into electrical energy. The operation of a generator is based on the principles discovered by Faraday. He found that when a magnet is moved past a conductor, it causes electricity to flow. In a large generator, electromagnets are made by circulating direct current through loops of wire wound around stacks of magnetic steel laminations. These are called field poles, and are mounted on the perimeter of the rotor. The rotor is attached to the turbine shaft, and rotates at a fixed speed of 3000 rpm. When the rotor turns, it causes the field poles (the electromagnets) to move past the conductors mounted in the stator. This, in turn, causes alternating current to flow at a frequency of 50 Hz, and a voltage to develop at the generator output terminals. The stator of the generator has 3 armature windings, at 120° of offset to each other, and this gives rise to our 3-phase electrical supply, with each phase at a frequency of 50 Hz and 120 degrees out of phase with the other 2 currents. This makes it possible for a steady stream of power to be delivered at a constant rate, making it possible to carry more load (i.e. current), and allows for greater conductor efficiency than single-phase.

The generators in Eskom's power stations produce electricity at ±20 000 volts (20kV). This voltage is raised by step-up transformers before it is sent out. The high voltage transmission system in Eskom comprises a 132 000, 275 000, 400 000 and 765 000 volt system. In order for electricity to be transmitted safely and efficiently over long distances in the network of overhead transmission lines (the National Grid), it must be at a high voltage and a low current. This is because if the current is too high, the lines would heat up too much and even melt (the heating effect of a current is given by $W= I^2R$). If the voltage were too low, hardly any energy would be carried.

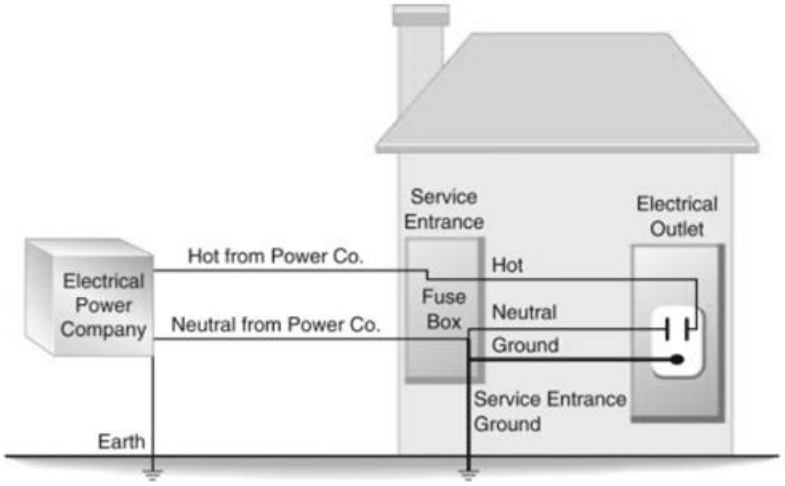
From the National Grid to local distribution to the home:

From the high voltage network, the electricity is transformed down, for example, to 11 000 volts for local distribution, and then to 220/230 V for domestic use in South Africa. The 220 V is the effective voltage, also called the root mean square, or RMS.

A typical power cord consists of two conductors. One, designated as *live* ("hot" in the USA; the brown wire when you wire an electrical plug) carries the current to the impedance; the other is *neutral* (the blue wire), and it returns the current to the source. The potential difference between the two is effectively 220 volts. In a *grounded* system, the *neutral* wire is intentionally connected to the ground by

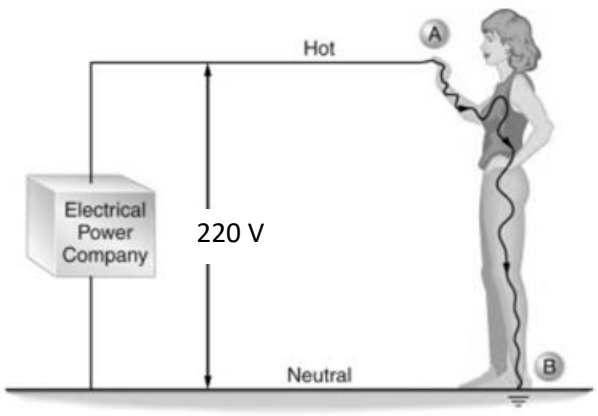
an *earth* wire (the green wire), which is at the same potential as the neutral wire. Eskom does this as a safety measure to prevent electrical charges from building up in their wiring during electrical storms, and to prevent the very high voltages used in transmitting power by the utility from entering homes in the event of an equipment failure in their high-voltage system. The ground is considered a current sink, meaning it can accept and carry virtually unlimited amounts of current.

The figure below shows the neutral grounded power supply to a typical home; note that there are the two lines, *live* and *neutral*. The neutral is connected to ground by the power company and again connected to a service entrance ground when it enters the fuse box. Both the *neutral* and *ground* wires are connected together in the fuse box at the neutral bus bar, which is also attached to the service entrance ground.



1) ELECTRICAL SHOCK

A shock is experienced when electric current passes through the body. The amount of current that flows will be a function of the voltage difference across the body and the resistance to current flow presented by the body. There must be a complete circuit for current to flow. Two points of contact must therefore exist for current to flow through the body. Oftentimes, one of these contacts is established as a result of standing on the ground, so only one other point of contact needs to be made in order for current to flow and a shock to occur. The primary objective in electrical safety is to prevent patients or staff from becoming a part of that complete circuit.



Ground* or *grounding: This refers to two separate concepts- the first being the grounding of electrical power, and the second being the grounding of electrical equipment. So, power can be grounded or ungrounded and power can supply electrical devices that are themselves grounded or ungrounded. *A*nything connected to ground, whether intentionally (e.g., an equipment case or the OR bed) or unintentionally (e.g., a patient or staff person contacting a source of electrical power) will be held at a reference voltage that is by definition 0 V. In addition, the connection to ground provides a low-resistance pathway that permits current to return to its source. Ideally, patients (and other individuals) should never be grounded, thus removing any possibility of becoming part of the electrical circuit.

However, this can be difficult and impractical to accomplish, so instead the entire OR is kept isolated from ground (see later). Conversely, electrical equipment should always be grounded, to provide a low-resistance pathway for current to return to its source, rather than through some alternate pathway, such as a person. For example, if a piece of equipment was not grounded, but it had a fault such that electrical power was in contact with the case, an individual coming into contact with that case would then serve as the sole pathway for the fault current to flow back to the source. By keeping the equipment grounded, the bulk of the fault current will be conducted by the ground connection and only a small portion will flow throw the person, thus significantly reducing the risk of shock.

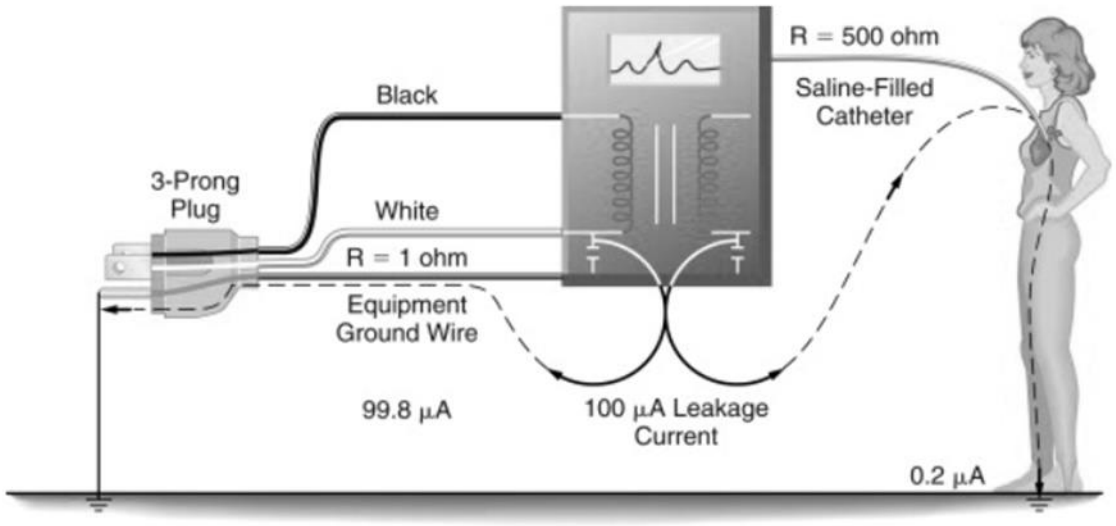
Current	Effect
Macroshock	
1 mA (0.001 A)	Threshold of perception
5 mA (0.005 A)	Accepted as maximum harmless current intensity
10–20 mA (0.01–0.02 A)	“Let-go” current before sustained muscle contraction
50 mA (0.05 A)	Pain, possible fainting, mechanical injury, heart and respiratory functions continue
100–300 mA (0.1–0.3 A)	Ventricular fibrillation will start, but respiratory centre remains intact
6,000 mA (6 A)	Sustained myocardial contraction, followed by normal heart rhythm; temporary respiratory paralysis; burns if current density is high
Microshock	
100 µA (0.1mA)	Ventricular fibrillation
10 µA (0.01mA)	Recommended maximum 60 Hz leakage current
1 A (amperes)	**=1,000 mA (milliamperes) =1,000,000 µA (microamperes)**

Injuries that result from electric shock include burns and tissue damage, ventricular fibrillation, and death (see above). The injury that occurs will depend on the magnitude and duration of current flow through the body, as well as the cross-sectional area through which it flows. This is embodied in the concept known as *current density*, which is defined as the amount of current flowing through a given cross-sectional area, and can be thought of as a measure of how “concentrated” the current is.

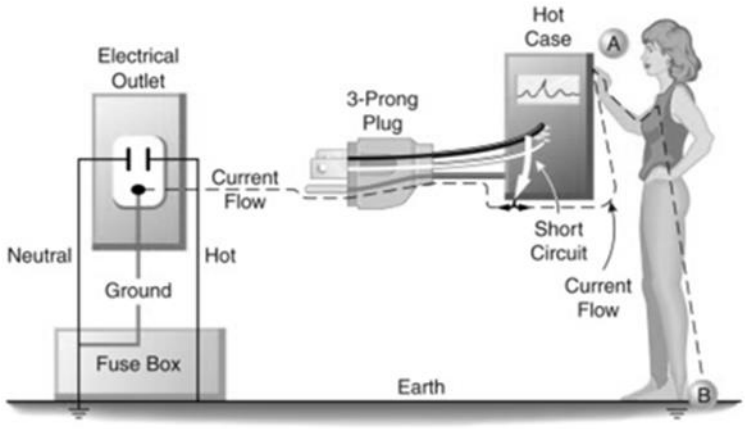
Macroshock refers to currents on the order of 1 mA or larger that are applied externally to the skin, that is, currents that are perceptible. There is a second phenomenon known as *microshock* that involves currents below the threshold of perception.

Microshock occurs in what is known as an *electrically susceptible patient*, that is, a patient with a direct conductive connection to the heart (e.g., a temporary pacemaker wire or a saline-filled catheter) that bypasses the skin. This is important as the skin is normally a source of considerable resistance. Not only does the direct connection provide a low-resistance pathway to current flow, the connection

contacts the heart in a very small area. As a result, despite the low current levels flowing (as low as 10-100 μA), the resulting current density is sufficient to cause ventricular fibrillation. Because the current levels associated with microshock are so low, below the threshold of perception, normal methods to detect hazardous situations and prevent shock don't work. For example, *line isolation monitors* (LIMs) (see below) do not help to protect against microshock. It is a functioning equipment ground wire that protects against microshock (**FIGURE below**).



Most ORs utilise power sources that are isolated from ground, that is, **isolated power supplies**. These differ from the grounded type of power supplies used in the home and other hospital locations in several important ways. A grounded power supply will have one live lead and one neutral lead, which is physically connected to the ground conductor. If a person (who is typically going to be in contact with ground) should come into contact with the electric circuit (e.g. by touching a faulty piece of equipment), there is a potential for some current to flow from the point of contact through the individual to ground and thus back to its source, as in the figure below.



Because the equipment is grounded, however, most of the current will flow along established low-resistance grounding pathways, and only a small fraction through the much-higher-resistance person.

In contrast, isolated power supplies provide electrical power through two leads, *line 1* and *line 2*, neither of which is connected to ground. The two lines are electrically isolated from ground by an isolation transformer located in the OR. Electrical equipment is still grounded through a third conductor; however, there is no pathway for current to flow from either line 1 or line 2 back to its

source via the ground. As a result, if a person in contact with ground comes into contact with either line 1 or line 2, there is no pathway for establishing a complete circuit, and no shock can result. Only if the individual comes into contact with both lines 1 and 2 does a complete circuit result, thereby allowing current to flow and a shock to occur. The use of isolated power supplies thus provides an added layer of protection against electrical shock.

FIGURE below: An isolated power supply

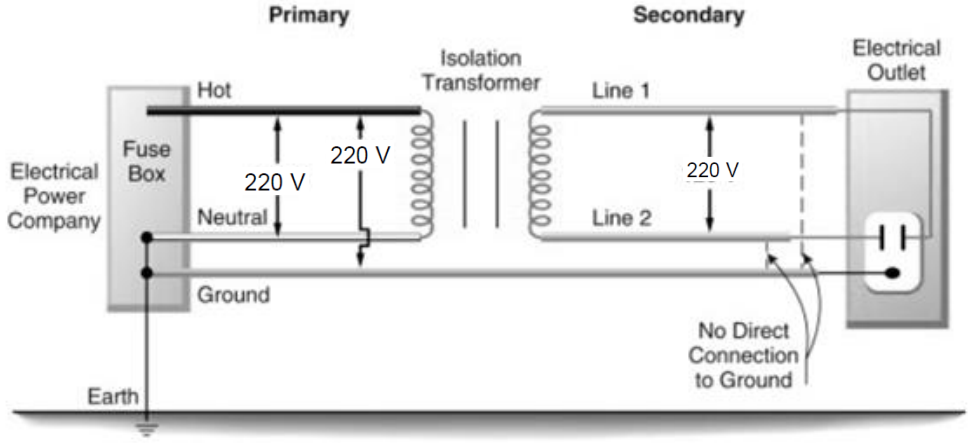
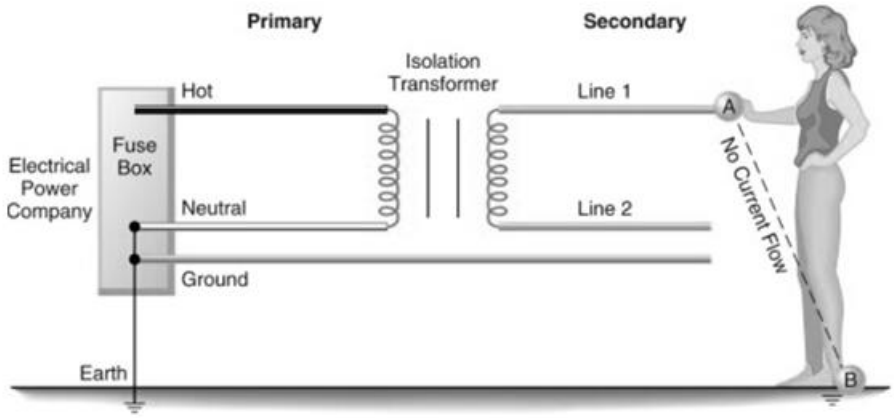


FIGURE below: A safety feature of the isolated power system is illustrated. An individual contacting one side of the isolated power system (point *A*) and standing on the ground (point *B*) will not receive a shock. In this instance, the individual is not contacting the circuit at two points and thus is not completing the circuit. Point *A* (*cross-hatched lines*) is part of the isolated power system, and point *B* is part of the primary or grounded side of the circuit (*solid lines*).



Isolation is not perfect, however, and leakage currents do exist. What is important is that the leakage can become significant enough to defeat the isolation, in which case the power supply changes from an isolated to a grounded supply.

This will not affect equipment function, nor does it cause a shock, but it does remove that extra layer of protection. Since equipment continues to function, such a change will go unnoticed. A *line isolation monitor* (LIM) is used to monitor the quality of the isolation from ground and will alarm if the impedance to ground drops low enough that significant current (5 mA) could flow.

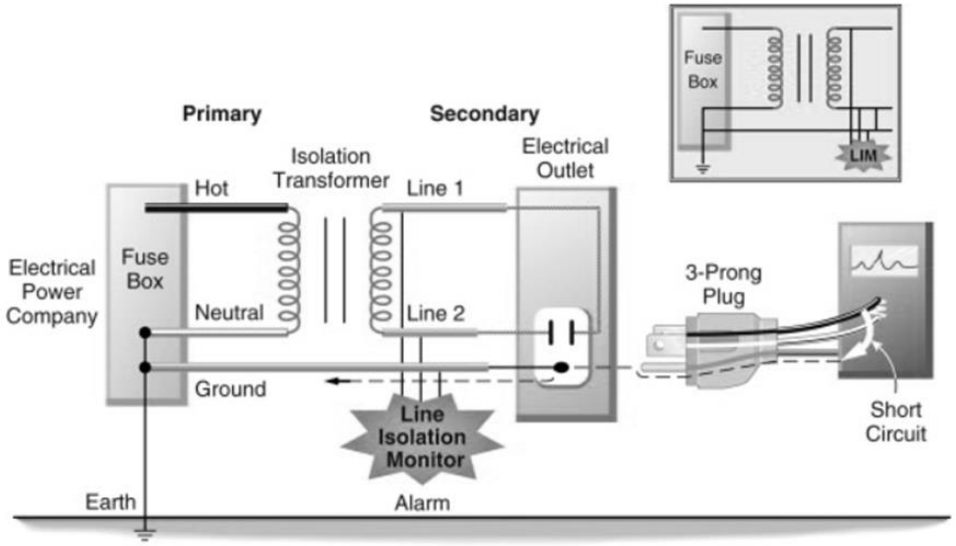


FIGURE above: When a faulty piece of equipment is plugged into the isolated power system, it will markedly decrease the impedance from line 1 or line 2 to ground. This will be detected by the LIM, which will sound an alarm.

The power grid supplies grounded power, with the neutral lead physically connected to the ground conductor. In the OR, after passing through an isolation transformer, line 1 and line 2 supply electrical power, but there is no connection with ground. Consequently, contact with either line 1 or line 2 cannot result in current return via the ground conductor. There are two ways in which isolation could fail. The first occurs when a piece of equipment has a “ground fault,” that is, when there is an unintended connection between either line 1 or line 2 and ground. The second way in which a system could lose isolation is if enough pieces of equipment, each with about 100 μA of leakage, are plugged into the supply. This would lower the impedance to the point of converting the isolated system to a grounded supply. As previously noted, in both situations equipment will continue to function normally, hence the need for the LIM.

If an LIM should alarm, the cause needs to be determined. Is it a faulty piece of equipment or just too many pieces of equipment? The recommended practice is to unplug equipment, one piece at a time, starting with the last piece plugged in. A faulty piece of equipment is likely to be associated with a larger change in the hazard current than just having too many items plugged in. If the cause for the alarm is still unclear, equipment can be taken to another room and plugged in; if faulty, it should alarm there, too. A faulty piece of equipment should be removed from service.

A significant advantage of the LIM is that equipment will continue to function, and critical life support functions will not be interrupted. An alternative piece of equipment that also protects against shock and ground faults is known as a *ground fault circuit interrupter* (GFCI). It differs in one important way from an LIM. Rather than an alarm that notifies the user that isolation has been overwhelmed, it stops the flow of current. Any electrical equipment connected to a circuit utilizing a GFCI will cease to function. This is an obvious disadvantage in situations where life support equipment is being used, and for that reason, these devices are not used in the OR.

ISO classification of medical equipment according to its *method* of protection against electric shock:

Class 1: Class 1 equipment has a protective earth. The basic means of protection is the insulation between live parts and the exposed conductive parts such as the metal enclosure. In the event of a fault which would otherwise cause the exposed conductive part to become live, the supplementary protection, i.e. protective earth, comes into effect. A large fault current will flow from the live wire to earth via the earth wire, which causes a protective device (usually a fuse) in the live wire to melt, disconnecting the equipment from the power supply.

Class 2: The method of protection here is either double insulation or reinforced insulation. In double insulated equipment, the basic protection is afforded by the first layer of insulation. If basic protection fails then supplementary protection is afforded by a second layer of insulation preventing contact with live parts. The symbol for Class 2 equipment is 2 concentric squares, indicating double insulation.

Class 3: Here, the protection against electric shock relies on the fact that no voltages higher than safety extra low voltage (SELV) are present. SELV is defined in the relevant standard as a voltage not exceeding 25 V AC or 60 V DC.

Type designation of equipment: describes the *degree* of protection, based on the maximum permissible leakage currents under normal and fault conditions. The reason for the existence of type designations is that different pieces of medical electrical equipment have different areas of application and therefore different electrical safety requirements. For example, it would not be necessary to make a particular piece medical electrical equipment safe enough for direct cardiac connection if there is no possibility of this situation arising.

Type B (Body): Type B classification is given to applied parts which are generally not conductive and may be connected to earth. May be any class (see above), but the maximum patient leakage current under normal conditions is 100 µA. There is the risk of microshock.

Equipment that is connected to patients (e.g. via surface electrodes) **must** be designated as type BF or CF.

Type BF (Body Floating): Type BF classification is given to applied parts which are electrically connected to the patient and must be floating and separated from Earth. This classification does not include applied parts which are in direct contact with the heart. Allowable leakage currents are as for Type B, but here a mini isolation transformer is employed to create an isolated circuit with no direct connection to the main circuit.

Type CF (Cardiac Floating): Type CF classification is given to applied parts suitable for direct cardiac connection. These parts must be floating and separated from earth. This equipment uses an isolated circuit; maximum patient leakage current under normal conditions is below 10 µA.

. **SYMBOLS**

Type B

Type BF

Type CF

2) BURNS

The amount of heat produced by current flow depends on the magnitude of the current and the resistance. A given current flowing through a small area will produce more heating than the same current flowing through a large area. The situation most commonly associated with burns in the OR is related to the use of an electrosurgical device (ESU or “diathermy”). Electric current passes from a “pencil” through the patient to a dispersive pad (often incorrectly called “the grounding pad”). Because the pencil tip is small, a high current density exists and significant heating occurs.

However, the dispersive pad occupies a much larger surface area, resulting in much lower current density, effectively protecting against skin burns. However, if the conductive gel is dried out, the pad is incorrectly applied so it does not make good contact with the skin throughout its entire surface, or it is removed and reapplied, current can be concentrated at the point(s) of contact, resulting in skin burns. Ideally, the pad will be applied over well-muscled areas, such as the thigh, arm, or buttocks. It should not be placed over hairy areas (it won’t stick well) and over bony prominences or metal prostheses (the current can be concentrated at these points), and it should not be reapplied if it is removed (insufficient gel may remain). Alternatively, current may seek other pathways, such as through ECG electrodes, again resulting in a high enough current density to cause burns.

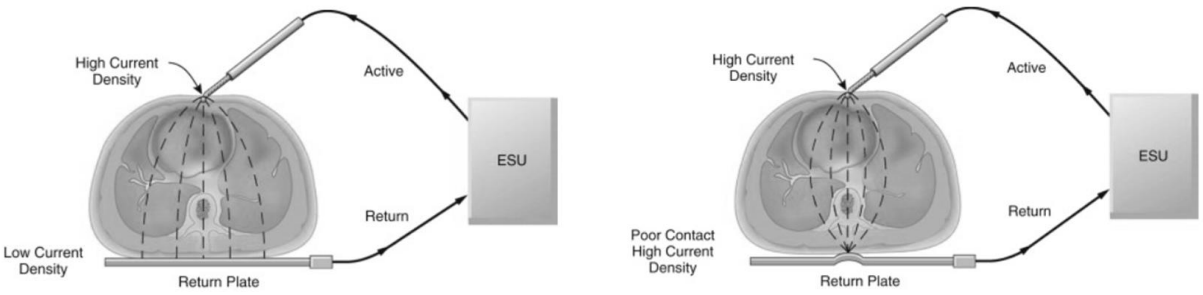


FIGURE above: A properly- vs an improperly-applied ESU return plate.

3) LOSS OF ELECTRICAL POWER

A loss of electrical power is a potentially catastrophic situation that requires prompt and effective management to minimize the risk to patients. The cause of an electrical power failure can be external to the institution, due to an interruption of the power company’s supply to the hospital, or to internal failures, which may affect only a portion of the facility. The risk to patients can result from equipment that stops functioning, for patients whose lives depend on critical life-support equipment, or from the interruption of and interference with surgery or other invasive procedures. As such, a power outage represents a very different problem than electrical shock.

Whereas shock will generally affect only a single patient, the loss of electrical power can affect many patients. Electric shock produces an immediate result, such as ventricular fibrillation, but the consequences of a power outage may extend over time. Finally, there is usually some form of backup electrical supply to maintain equipment function in the event of an outage. This can take the form of a battery, such as in the anesthesia machine, or hospital generators.

Should there be a loss of power, several issues must be considered. First, patient status must be ascertained. Second, the status of the anaesthetic and the surgery must be established. If the surgical procedure must continue, how will the anaesthetic be provided? It is possible to use a portable monitor, intravenous infusion pumps to provide a total intravenous anaesthetic, oxygen from tanks,

and ventilation via an Ambu-bag, and these will all potentially need to be sourced in the case of a power failure during an operation.

Light can be provided from torches and laryngoscopes. All OR personnel should be familiar with the location of emergency light sources. Nonetheless, if it appears that the power outage will be of significant duration, steps should be taken to conclude the surgical procedure. Third, equipment function needs to be evaluated. The status of the anaesthetic machine, monitors, light sources, and any powered surgical equipment must be clarified, so decisions about whether or not to continue surgery can be made. Finally, and perhaps most importantly, the scope and duration of the outage must be determined. Is it confined to a single OR, to a collection of ORs, or to some larger entity, such as one or more floors, the hospital or facility, or an entire community? The expected duration of the interruption in power must be determined, as it will significantly influence decision making.

It is important to realize that having backup power is no guarantee of continued operations. There have been several instances where the backup supply has failed, resulting in the OR, or institution, being completely without power.

Because a loss of power may occur, it is necessary to know which items of equipment have internal battery backup. It's important to keep the batteries fully charged and to know how long the backup batteries will last; what functions will continue on backup power; how to provide light, computer, phone, and paging services; and how to provide alternatives to primary equipment and functions (e.g., portable monitors in place of normal physiologic monitors, or intravenous anesthesia via infusion pumps in place of inhaled anesthetics delivered by the anesthesia machine).

In addition, it is important to understand how electrical power is provided to the OR, that is, which sockets are intended to function only under normal conditions (usually white sockets), and which will provide emergency power in the event of a power failure (usually red sockets). Essential equipment, such as anaesthesia machines, should always be plugged into emergency (red) sockets.

4) IMPLANTED DEVICES

The fourth and final category of electrical hazard has to do with patients who have implanted electronic devices, such as pacemakers, implantable cardioverter-defibrillators (ICDs), cochlear implants, and spinal cord or other stimulators. The risk is that these devices may be damaged or malfunction as a result of exposure to electrical currents, which may result in harm or death.

The malfunction of pacemakers and ICDs due to electromagnetic interference from electrosurgical devices poses the greatest risk to patients. The typical reason for malfunction is that electrical currents from the electrosurgical unit pass in proximity to the implanted device or leads emanating from it, resulting in a change to the device's mode of operation (reprogramming), accidental firing of an ICD or stimulator, or damage to the device. Simple steps can usually prevent this from being a problem. The dispersive pad should be placed so the current does not cross the device, but instead travels away from it. For example, if a patient has a pacemaker on the left side of the chest, and surgery is being conducted on the right shoulder, the dispersive pad should not be placed on the left shoulder, or anywhere on the left side.

Bipolar electrosurgical devices should be considered in place of the usual monopolar device, as this will confine the current between the tips of the bipolar device. ICDs should be programmed OFF for the duration of surgery, and reprogramming can be used to convert pacemakers to an asynchronous mode of function.

References:

1. **Part 1 ARC 2010** – chapter on Electrical safety by Prof Ivan Joubert

2. **Anesthesia Equipment: Principles and Applications,** 2nd edition, 2013- Ehrenwerth, J; Eisenkraft, J; and Berry, J.
   The use of diagrams from this source is gratefully acknowledged.

Calcium, Magnesium and Phosphate

Dr Revyl Haylett

Dept of Anaesthesia & Perioperative Medicine
University of Cape Town

CALCIUM AND PHOSPHATE

Calcium circulates in different forms in the plasma: approximately 40% is bound to albumin, 15% to citrate, sulphate or phosphate; and 45% exists as a free fraction in its ionised form. The routine laboratory tests measure the free and bound forms. Plasma phosporus exists in organic and inorganic forms: as either phospholipids or ester phosphates, or as inorganic phosphates which are completely ionised as HPO_4^{2-} or $H_2PO_4^-$.

Only a small fraction of total body calcium and phosphate is located in the plasma but it is these plasma concentrations that are under hormonal control. Calcium balance is mediated by parathyroid hormone (PTH) and calcitriol (1,25 dihydroxyvitamin D) which control GIT absorption, bone formation and resorption, and urinary excretion. Phosphorus is also regulated by PTH, as well as a fibroblast growth factor (FGF) and its cofactor, which work separately and together to control renal phosporus excretion.

Renal handling of calcium

Only free, ionised calcium is filtered by the glomerulus, and nearly the entire amount is reabsorbed in subsequent segments of the nephron. Approximately 70% is reabsorbed passively along with sodium in the proximal convoluted tubule. A further 20% is reabsorbed in the thick ascending limb of the loop of Henle via a passive paracellular pathway mediated by tight junction proteins and assisted by a positive voltage in the lumen of the tubule *(c.f renal handling of magnesium)*.

The remaining 10% is reabsorbed in the distal convoluted tubule via an active, transcellular process. Calcium enters the cells via a receptor-linked calcium channel on the apical surface of the lumen cells. Once inside the cell, it binds to the *calbindin* protein which carries it to the basolateral cell surface where it is extruded into the circulation via two channels: a Na/Ca exchanger and a Ca-ATPase.

GIT handling of calcium

Dietary calcium is absorbed via two mechanisms: an active transcellular pathway via a receptor-linked calcium channel on the apical membrane of luminal cells in the duodenum and proximal jejunum; and paracellular transport occurring throughout the length of the intestine. However, this calcium absorption is incomplete due to a further two factors: activated calcitriol is required for intestinal calcium absorption; and once inside the intestinal lumen, calcium binds to anions to form insoluble calcium salts like *calcium phosphate* and *calcium oxalate* that are not absorbed.

Bone handling of calcium

The majority of body calcium and phosphate stores exist in bone as *hydroxyapatite*. Bone acts as reservoir for calcium and phosphate, and plasma levels are regulated by the selective release and reuptake of these minerals by the bone which is, in turn, under the hormonal control of PTH and calcitriol via the relative activity of osteoclasts and osteoblasts.

Parathyroid hormone (PTH)

This hormone is secreted by the parathyroid glands in response to decreases in plasma free, ionised calcium levels. The change in the plasma calcium level is sensed by the calcium-sensing receptor (CaSR) on the parathyroid cells and stimulates PTH release. PTH works to increase plasma calcium by:

- **Renal absorption** – PTH increases calcium reabsorption in the distal tubule by activating adenylyl cyclase ➔ increasing cAMP ➔ protein kinase A ➔ phosphorylates and activates the

receptor-linked calcium channels lining the lumen of the tubule. It also increases the expression of the intracellular calcium transport proteins mentioned previously.
- **Increased intestinal absorption** – PTH promotes renal formation of calcitriol which is required for effective intestinal calcium and phosphate reabsorption.
- **Bone resorption** – PTH mobilises skeletal calcium by binding to PTH receptors on osteo*blasts* to increase osteo*clast* number and activity to enhance bone resorption. PTH also binds directly to osteo*clasts* to achieve the same result.

Small elevations in plasma calcium concentration act as a negative feedback mechanism by binding to parathyroid CaSRs to decrease PTH secretion. Increasing levels of calcitriol also inhibit the production and secretion of PTH; as well as its own production, by inhibiting the action of 1αhydroxylase and increasing the production of 24αhydroxylase.

Calcitriol/Vitamin D

7 dehydrocholesterol + ultraviolet light ➔ Vitamin D3 (cholecalciferol) ~ synthesised in the skin

Vitamin D3 (cholecalciferol) + 25 hydroxylase ➔ 25 hydroxyvitamin D (calcidiol)

25 hydroxyvitamin D (calcidiol) enters the circulation, is filtered by the glomerulus and reabsorbed by the distal tubule. At this site, either:

25 hydroxyvitamin D (calcidiol) + 1αhydroxylase ➔1,25 dihydroxyvitamin D (calcitriol) ~ ACTIVE

OR

25 hydroxyvitamin D (calcidiol) + 24αhydroxylase ➔ 24,25 dihydroxyvitamin D ~ INACTIVE

Calcitriol increases plasma calcium levels by:

- **Renal reabsorption** – increasing the expression of the receptor-linked calcium channels and calbindin proteins in the distal tubule.
- **Intestinal absorption** – increasing the expression of similar GIT-associated receptor-linked calcium channels.
- **Bone resorption** – unclear mechanism, thought to be similar to that of PTH.

Phosphate handling and regulation

Absorption of phosporus in the GIT occurs via sodium-dependent (likely regulated by calcitriol) and sodium-independent pathways (unregulated). The majority of phosphate in the body is stored in bone as hydroxapatite, as mentioned earlier, and, like calcium, is released under the control of PTH. Phosphate release is also separately regulated by a fibroblast growth factor and its co-factor.

Gut absorption and bone release of phosphate determine the ultimate phosphate load presented to the kidneys to handle further. Phosphate is filtered at the glomerulus and approximately 80% reabsorbed, the majority of which is reabsorbed in the proximal tubule via transport proteins linked to three separate sodium co-transporters.

It is this renal threshold for phosphate reabsorption in the proximal tubule that is important in determining the steady state of serum phosphate concentration. Thus, PTH and FGF may mobilise phosphates along with calcium which may initially increase serum phosphate levels but are also the two dominant *phosphaturic* hormones.

Physiological actions of calcium

Calcium acts within the body as a universal second messenger system that activates and regulates a wide range of cellular activity: muscle contraction, mitochondrial enzymes, hormone and neurotransmitter release. In order to have such potent action, intracellular calcium levels need to be tightly controlled and are kept very low to maintain a large gradient across the cell membrane. A similarly large gradient exists between the cytosolic calcium concentration and that within the

intracellular organelles. The fluxes in calcium across these membranes are controlled by a series of ion channels, pumps, binding proteins and exchangers.

Control of intracellular calcium

Calcium **can enter the cell** through voltage-operated calcium channels (VOCC) following depolarisation in excitable tissue. Receptor-operated calcium channels (ROCC) allow calcium into the cell in response to the binding of a ligand to the receptor. Store-operated calcium channels (SOCC) are controlled by the calcium concentration within the ER: when the levels are low, SOCC channels in the ER near the cell membrane open to allow calcium to enter.

The release of calcium from these internal stores is mediated by the activation of either inositol triphosphate receptors (IP_3) or ryanodine receptors (RYR). Both these types of receptors may be, themselves, activated by calcium – so-called *calcium induced calcium release* (CICR).

A rise in intracellular calcium results in the activation of ATPases to release energy to pump calcium out of the cell, into the mitochondria and into the endoplasmic reticulum (ER).

The main mechanism for calcium extrusion **out of the cell** is the high capacity, low affinity Na^+/C^{2+} antiporter, exchanging sodium for calcium. This pump is driven by the sodium gradient across the cell membrane which is, in turn, maintained by the Na/K ATPase pump. The low capacity, high affinity $Ca^{2+/}H^+$ ATP-dependent exchanger works to fine tune the intracellular calcium concentration. Calcium can also bind to calcium-binding proteins (CaBP) which may activate other cellular processes, such as calmodulin, or simply act as buffers, like the calbindins.

Mitochondria have a high capacity for calcium but excessive accumulation may bind phosphate, inhibiting ATP production and ultimately damaging the organelle.

The **endoplasmic reticulum (ER)**, or sarcoplasmic reticulum (SR) in muscle cells, is the major site of intracellular calcium storage, and the chief source of rapid calcium release in response to transient stimulation. Rising intracellular calcium levels stimulate similar mechanisms used to extrude calcium out of the cell, to drive calcium into the ER where it exists in both its free and bound state.

Inositol triphosphate IP_3 and diacylglycerol DAG

Ligand + G-protein coupled receptor
↓
Activates phospholipase C
↓
acts on membrane-bound phosphatidyl-inositol bisphosphonate (PIP_2)
↓
releases IP_3 and DAG

IP_3 binds to its receptor on the ER/SR to open the channel and release calcium. IP_3 is rapidly metabolised which limits the duration of the signal, but the extent may be 'amplified' by the successive stimulation of the receptors creating a wave of calcium and IP_3 that can move through the cytosol and across cells via gap junctions.

DAG directly activates protein kinase C creating a parallel and sustained signal transduction cascade.

Control of calcium in skeletal muscle

The excitation-contraction coupling unit of skeletal muscle is the triad consisting of the t-tubule and two terminal cisterns of the SR. Depolarisation of the sarcolemma by the action potential directly activates the dihydropyridine receptors (DHPR) which activate the RYRs which release calcium from the SR into the cytosol. Calcium binds to troponin C to initiate contraction, and binds to calmodulin to increase cellular metabolic rate and energy production through glycogenolysis. The rising cytosolic calcium activates ATPases that pump calcium back into the SR where it binds to calsequestrin, a CaBP.

Control of calcium in cardiac muscle

The excitation-contraction coupling unit of cardiac muscle consists of the t-tubule, a L-type (long acting) calcium channel DHPR, and one terminal cistern of the SR. Depolarisation of the sarcolemma by the action potential activates the L-type DHPR to open and admit calcium. This causes a plateau phase of the action potential. Calcium influx stimulates calcium release via the RYRs to in turn release calcium from the SR (CICR) to initiate contraction and energy production. The rising cytosolic calcium activates ATPases that pump calcium back into the SR where it binds to calsequestrin. This process is facilitated by the phosphorylation of phospholamban by cAMP.

Control of calcium in smooth muscle

Vascular smooth muscle cells employ a mechanism similar to cardiac cells: calcium entry via VOCCs is amplified by CICR from the SR. However, this process is much less efficient in smooth muscle cells and so the generation of a calcium signal is much more dependent on the entry of extracellular calcium.

Depolarisation of the cell membrane need not take place as calcium can enter the cells via ROCCs, and the response may be sustained as the DAG messenger system can be employed. DAG directly activates protein kinase C which maintains contraction through phosphorylation of myosin light chain kinase or via sustained calcium cycling across the cell membrane.

MAGNESIUM

Magnesium balance is a function of intake and excretion. The average daily magnesium intake is 360mg, with a third being absorbed in the small bowel via either a saturable transport system or by passive diffusion. About 40mg is secreted as a part of intestinal secretions, whilst half that may be absorbed again in the large bowel.

Changes in magnesium intake are balanced by changes in urinary magnesium reabsorption (mainly in the loop of Henle and distal convoluted tubule). The gain and loss of magnesium from bone is a zero sum, so the overall magnesium homeostatic level is due to the variable renal excretion of the approximately 100mg that is absorbed in the GIT.

Renal handling of magnesium

Almost all of total plasma magnesium is filtered at the glomerulus, with less than a fifth being reabsorbed passively down a concentration gradient in the proximal tubule and even less in the distal tubule. The major site of magnesium transport is the thick ascending limb of the loop of Henle where the majority is reabsorbed.

The passive transport occurs via paracellular diffusion and is driven by a favourable electrical gradient resulting from the reabsorption of sodium chloride and a positive intra-luminal charge. This lumen-positive voltage is generated by two processes:

- Reabsorption of sodium, potassium and chloride via a co-transporter, with potassium recycling back into the lumen.
- Net reabsorption of sodium chloride dilutes the tubular fluid and generates a concentration gradient towards the thick ascending limb of the loop of Henle. This favours a backflux of sodium choride into the tubular space, with a theoretical paracellular pathway that favours sodium over chloride resulting in the lumen-positive voltage and augmenting magnesium reabsorption.

Factors controlling magnesium transport act through changes in the voltage and/or permeability of the paracellular pathway. Magnesium wasting can be induced by the administration of a loop diuretic which inhibits sodium and chloride reabsorption; or by genetic mutations to the tight-junction proteins between renal tubule cells involved in paracellular diffusion allowing magnesium reabsorption.

Other factors affect magnesium transport in the loop of Henle:

- **Plasma magnesium concentration –** this is the main physiological regulator of urinary magnesium excretion. Hypermagnesaemia inhibits loop magnesium (and calcium) reabsorption, whilst hypomagnesaemia stimulates it.
- **Plasma calcium concentration –** hypercalcaemia inhibits magnesium (and calcium) reabsorption. A calcium-sensing receptor in the thick ascending limb of the loop of Henle activates a complex signalling sequence that ultimately inhibits the expression of the tight-junction proteins and thus, magnesium reabsorption.
- **Hormones –** parathyroid hormone, calcitonin, glucagon, arginine vasopressin and beta-adrenergic agonists work via adenylate cyclase to increase the lumen-positive voltage and the paracellular permeability, altering magneisum transport but not playing a role in normal magnesium homeostasis
- **Other factors –** metabolic alkalosis stimulates magnesium reabsorption; metabolic acidosis, hypokalaemia and hypophosphataemia inhibit magnesium reabsorption. The mechanisms are unknown.

Regulation of plasma magnesium concentration

As alluded to previously, there are no hormones directly involved in regulating urinary magnesium excretion, with one paper going so far as to describe it as an ‘orphan’ element. Bone is the principal reservoir of magnesium and does not readily exchange with circulating magnesium. This inability to easily mobilise the magnesium stores means that, with a negative magnesium balance, the initial losses come from plasma magnesium and equilibration with the bone stores occurs only after several weeks. Plasma magnesium levels fall quickly and lead to a marked reduction in urinary magnesium excretion. The fractional excretion of magnesium, normally 3-5%, can fall below 0.5%.

There is also no protection against hypermagnesaemia with loss of renal function. Continued intake leads to elevated magnesium levels in the extracellular fluid.

Intracellular magnesium stores and activity

The total intracellular magnesium content is 8-10mmol/L but the free cytosolic concentration has been measured as 0.6-0.8mmol/L, indicating that most of the magnesium is bound to ATP and other nucleotides and enzymes. Changes to plasma magnesium concentration alter the intracellular levels slowly. Magnesium enters the cell via a favourable electro-chemical gradient; but movement out of the cell is energy-dependent, probably via a Na/Mg/ATP exchanger.

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Notes:

The Bohr and Haldane Effects

Dr Kobus Bergh

Dept of Anaesthesia & Perioperative Medicine
University of Cape Town

The Bohr and Haldane effects have got to do with the loading of oxygen to the haemoglobin molecule and the unloading of oxygen from the haemoglobin molecule [6]. Just in case you were wondering, both these effects got their names from the people who described them.
I will first discuss some essential theory that is needed to understand these effects, before exploring them in detail.

Essential knowledge needed to understand the Bohr and Haldane effects

Some essential facts about Haemoglobin [1,2,7]

Haemoglobin is the red, O_2 carrying pigment in the red blood cells (erythrocytes) of vertebrates. There are about 200 – 300 million haemoglobin molecules in each red blood cell.

Haemoglobin is a protein and this protein is made up of 4 subunits (Fig.1). Each subunit contains a *haem moiety* attached to a polypeptide chain. (Definition of moiety = a distinct part of a large molecule). The *haem moiety* is a complex made up of a porphyrin and a central iron atom in the ferrous state (Fe^{2+}). The polypeptides are referred to collectively as the *globin portion* of the haemoglobin molecule. Some finer detail to take note of, is that the *haem moiety* is attached (at a constant distance) to a histidine group on the *globin portion*, and this forms one subunit of haemoglobin.

There are 2 pairs of polypeptides in each haemoglobin molecule. In normal adult human haemoglobin (HbA), the 2 types of polypeptides are called ***α chains***, (each α chain contains 141 amino acid residues), and ***β chains***, (each β chain contains 146 amino acid residues).

Each of the 4 iron atoms can bind reversibly to 1 molecule of oxygen, and therefore each haemoglobin molecule can bind to 4 oxygen molecules. Bear in mind that the iron stays in the ferrous state, so that the reaction is an oxygenation, not an oxidation!

HbA can have its ferrous ion (Fe^{2+}) oxidized to the ferric form (Fe^{3+}) by drugs and chemicals such as prilocaine, nitrates, nitrites, sulfonamides, and acetanilid. Deficiency of the enzyme methaemoglobin reductase within the red blood cell who's job it is to convert Fe^{3+} to Fe^{2+} may also cause this. When the iron atom is in its ferric form it is known as methaemoglobin and methaemoglobin is unable to carry oxygen. [1,7]

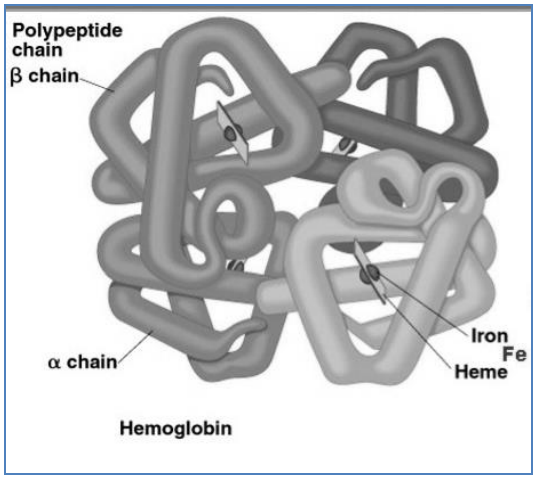

Fig. 1. Haemoglobin A

Image from:
https://bhavanajagat.com/2013/10/26/wholedude-wholedesigner-red-blood-cell

Oxygen transport in the blood [1,7]

It is important to appreciate that oxygen is carried in blood in two forms: *Dissolved* and *combined with haemoglobin (Hb).*

Dissolved oxygen

- Like all other gasses, oxygen obeys Henry's Law, which states that the gas dissolved in a liquid is proportional to its partial pressure.
- For each mmHg of P_{O_2}, there is 0,003 ml O_2 dissolved per 100 ml of blood at 37°C.
- Therefore arterial blood with a P_{O_2} of 100 mmHg (13,3 kPa) contains 0,3 ml O_2 per 100 ml.
- It is clear that this way of transporting oxygen is inadequate and that an additional method for transporting oxygen is required…!

Combined with haemoglobin

- I have discussed most of this already under Haemoglobin.
- Take note that oxygen bound to Hb does not contribute directly to the P_{O_2} of the blood, only dissolved oxygen contributes to P_{O_2}.
- At normal atmospheric pressure, 98% of oxygen in blood is bound by Hb.

The reaction of Haemoglobin and Oxygen [2,3,7]

The quaternary structure of haemoglobin determines its affinity for O_2. The change in Hb from the fully oxygenated state to its deoxygenated state is accompanied by a conformational change in the molecule. The oxygenated form is the *R (relaxed) state*, while the deoxygenated form is the *T (tense) state*.

In de-oxyhaemoglobin, the globin units are tightly bound in a *tense (T) configuration*, which reduces the affinity of the molecule for O_2. When O_2 is first bound, the bonds holding the globin units are released, producing a *relaxed (R) configuration*, which exposes more O_2 binding sites. The net result is a 500-fold increase in O_2 affinity! In the tissues these reactions are reversed and O_2 is released.

The oxygen-haemoglobin dissociation curve is a curve that plots oxygen saturation of haemoglobin against P_{aO_2}. It has its characteristic sigmoid shape due to the T-R interconversion. Combination of the first haem in the haemoglobin molecule with O_2 increases the affinity of the second haem for O_2, and oxygenation of the second, increases the affinity of the third and oxygenation of the third increases the affinity of the fourth! Therefore the affinity of haemoglobin for the fourth O_2 molecule is many times that for the first.

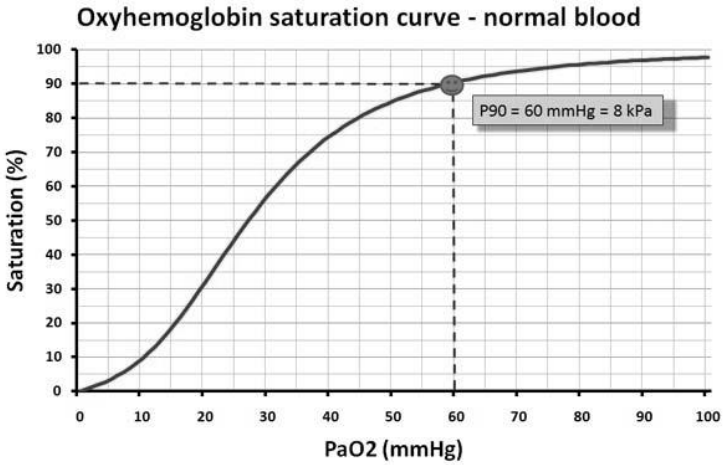

Fig. 2. The Oxygen-haemoglobin dissociation curve

Image from:
http://engineering.stackexchange.com/questions/3058/how-to-generate-a-synthetic-infrared-and-red-led-signal-for-spo2-calculation

Factors affecting the affinity of Haemoglobin for Oxygen [2, 7]

Five important conditions affect the oxygen-haemoglobin dissociation curve:

- the **pH**
- the **hydrogen ion** concentration
- the amount of **CO_2**
- the **temperature**
- the concentration of **2,3 diphosphoglycerate (2,3 DPG)**.

A rise in temperature or a fall in pH shifts the curve to the right (Fig 3). A rightward shift means more unloading of oxygen at a given P_{O_2} in a tissue capillary. A simple way to remember these shifts is that an exercising muscle is acidic, hypercarbic, and hot, and it benefits from increased unloading of oxygen from its capillaries. When the curve is shifted to the right, a higher P_{O_2} is required for

haemoglobin to bind a given amount of O_2. On the other hand, a fall in temperature or a rise in pH shifts the curve to the left, and a lower P_{O_2} is required to bind a given amount of O_2. A convenient index of such shifts is the P_{50}. The P_{50} is the P_{O_2} at which haemoglobin is half saturated with oxygen. The higher the P_{50} the lower the affinity of haemoglobin for oxygen.

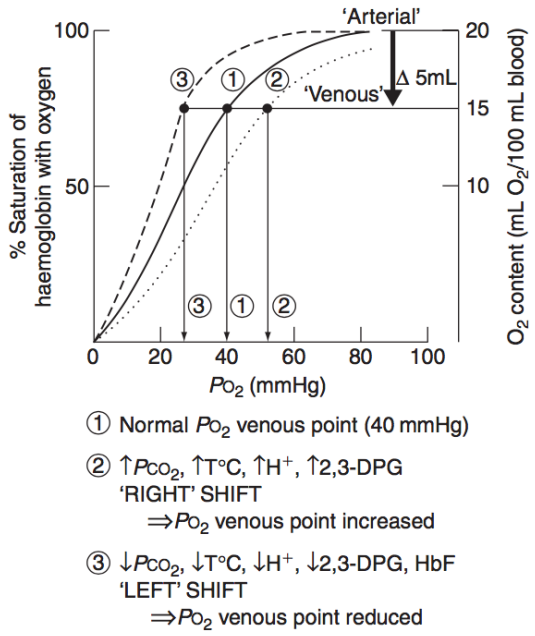

Fig. 3. Graphical representation of the Bohr effect.

Image from:
Power I, Kam P. Chapter 3: Respiratory physiology
Principles of Physiology for the Anaesthetist, second edition. Hodder Arnold

Carbon dioxide transport in the blood [2, 7]

It is important to know that CO_2 is carried in blood in the following three forms:

1. Dissolved (in plasma and RBC)
2. Bicarbonate (in plasma and RBC)
3. In combination with proteins as carbamino compounds (in plasma and RBC)

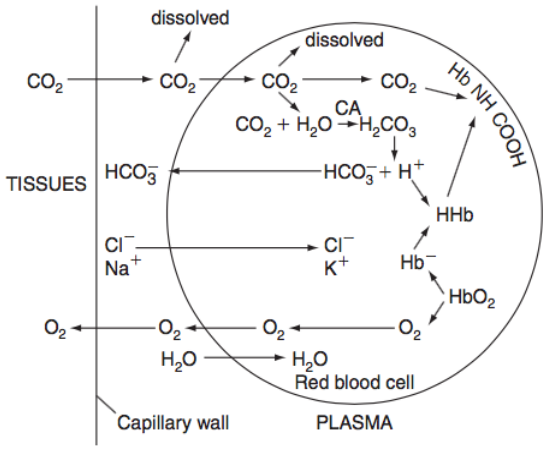

Fig. 4. Diagramatic representation of the uptake of CO_2 and liberation of O_2 in systemic capillaries

Image from:
Power I, Kam P. Chapter 3: Respiratory physiology
Principles of Physiology for the Anaesthetist, second edition. Hodder Arnold

1. Dissolved CO_2:

Like O_2, CO_2 also obeys Henry's Law. CO_2 is however about 20 times more soluble than O_2 in simple solution at equal partial pressures. As a result, dissolved CO_2 plays a significant role in its carriage in blood. About 10% of the gas that is evolved into the lung from the blood is in the dissolved form.

2. Bicarbonate:
Bicarbonate is formed in the blood by the following sequence:

$$CO_2 + H_2O \overset{\text{CA (carbonic anhydrase)}}{\leftrightarrows} H_2CO_3 \rightleftarrows H^+ + HCO_3^-$$

The CO_2 that diffuses into red blood cells is rapidly hydrated to H_2CO_3. The fist reaction is very slow in plasma but is fast within the red blood cell, because of the presence of the enzyme carbonic anhydrase (CA) in the red blood cell. The second reaction, which is the ionic dissociation of carbonic acid to form H^+ and HCO_3^- is fast without an enzyme!

What happens to the formed HCO_3^-?
Well, this is the ideal place to discuss the Chloride Shift…

The Chloride Shift (Hamburger phenomenon)
The rise in the HCO_3^- content of red cells is much greater than that in plasma as the blood passes through the capillaries, and about 80% of the HCO_3^- formed in the red blood cells diffuses out into the plasma. H^+ cannot easily diffuse out because the red cell's membrane is relatively impermeable to cations. Therefore to maintain electrical neutrality, Cl^- ions move into the red blood cell from the plasma. This is the so-called chloride shift, also known as the Hamburger phenomenon, named after Hartog Jakob Hamburger. The chloride shift is responsible for the fact that the chloride content of the red cells in venous blood is significantly greater than in arterial blood. The chloride shift occurs rapidly and is essentially complete in 1 second. For each CO_2 molecule added to a red cell, there is an increase of one osmotically active particle, either an HCO_3^- or a Cl^- in the red cell. Consequently the red cells take up water and increase in size! When the cells pass through the lung again they shrink a little!

What happens to the formed H^+?
Some of the H^+ ions bind to de-oxyhaemoglobin, which is illustrated below.

$$H^+ + HbO_2 \leftrightarrows H^+ - Hb + O_2$$

This occurs because de-oxyhaemoglobin is less acidic and is therefore a better proton acceptor than the oxygenated form. The presence of de-oxyhaemoglobin in the peripheral blood helps with the loading of CO_2, while the oxygenation that occurs in the pulmonary capillary assists in the unloading. The fact that deoxygenation of the blood increases its ability to carry CO_2 is known as the Haldane effect. (I will explain the Haldane effect in much more detail later!)

3. Carbamino compounds:
Carbamino compounds are formed by the combination of CO_2 with terminal amine groups in blood proteins. The most important protein is the globin of haemoglobin, and is illustrated by the following reaction:

$$Hb\text{-}NH_2 + CO_2 \rightleftarrows Hb\text{-}NH\text{-}COOH \text{ (This is carbamino-haemoglobin)}$$

This reaction occurs rapidly without an enzyme, and de-oxyhaemoglobin ($Hb\text{-}NH_2$) can bind more CO_2 to form carbamino-haemoglobin (Hb-NH-COOH) than oxyhaemoglobin (HbO_2). I hope that it is clear to you that the unloading of O_2 in peripheral capillaries facilitates the loading of CO_2, while oxygenation in the lungs has the opposite effect.

A last word on CO_2 carriage…
The greatest bulk of the CO_2 is in the form of bicarbonate (80 - 90%). The amount of dissolved CO_2 is small (5 - 10%), as well as the amount of CO_2 carried as carbamino-haemoglobin (5 - 10%).

Summary of Carbon Dioxide Transport [2]

In Plasma	*In Red Blood Cells*
1. Dissolved 2. Formation of carbamino compounds with plasma proteins 3. Hydration, H^+ buffered, HCO_3^- in plasma	1. Dissolved 2. Formation of carbamino-Hb 3. Hydration, H+ buffered, large% of HCO3- enters the plasma 4. Cl- shifts into cells

Of the approximately 49 ml of CO_2 in each 100 ml of arterial blood, 2,6 ml is dissolved, 2,6 ml is in carbamino compounds, and 43,8 ml is in HCO_3^-. In the tissues 3,7 ml of CO_2 per 100 ml of blood is

added; 0,4 ml stays in solution, 0,8 ml forms carbamino compounds, and 2,5 ml forms HCO_3^-. The pH of the blood drops from 7,40 to 7,36. In the lungs, the process is reversed, and 3,7 ml of CO_2 is discharged into the alveoli. In this fashion, 200 ml of CO_2 per minute at rest and much larger amounts during exercise are transported from the tissues to the lungs and excreted.

CO_2 Dissociation curve [1,7]

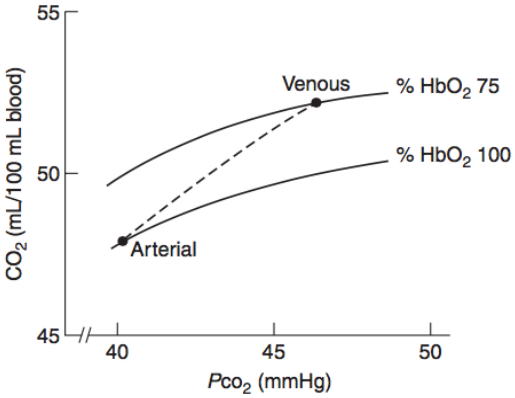

Fig. 5. The carbon dioxide-blood dissaciation curve

Image from:
Power I, Kam P. Chapter 3: Respiratory physiology
Principles of Physiology for the Anaesthetist, second edition. Hodder Arnold

In contrast to the dissociation of oxygen from haemoglobin, the dissociation of CO_2 from blood is directly related to the PCO_2 and therefore the dissociation curve for CO_2 is linear. Note also that the lower the saturation of Hb with O_2, the larger the CO_2 concentration for a given PCO_2. This is the Haldane effect, and a detailed explanation will follow later.

The Bohr effect… [1,2 4, 6]

The decrease in oxygen affinity of haemoglobin when the blood pH falls is called the Bohr effect and is related to the fact that de-oxygenated haemoglobin binds H^+ more actively than oxyhaemoglobin.

The pH of blood falls as its CO_2 content increases, so that when the PCO_2 rises, the oxygen haemoglobin dissociation curve shifts to the right and the P_{50} rises. Note that most of the unsaturation of haemoglobin that occurs in the tissues is secondary to the decline in the PO_2, but an extra 1-2% of haemoglobin's unsaturation is due to the rise in PCO_2 and the consequent shift of the dissociation curve to the right (Fig. 3)

The Bohr effect takes place in tissues that are metabolically active, for example in the quadriceps muscles when you are walking! As I have mentioned earlier, this magnificent piece of physiology helps with the unloading of oxygen from the haemoglobin molecule and it does so proportionally to the metabolic activity of the tissue. As more metabolism takes place, the carbon dioxide partial pressure increases and will cause larger reductions in local pH and in turn will allow for greater oxygen unloading. This is especially true in exercising skeletal muscles which may also release lactic acid that further reduces local blood pH and therefore enhances the Bohr Effect.

Now its time for a simplified explanation [6], some parts of this explanation has been discussed under the carriage of CO_2 already, but repetition is good…!
Imagine an individual quadriceps muscle cell in which CO_2 will be produced due to the Krebs cycle in the mitochondria. The produced CO_2 will diffuse out of the muscle cell down a partial pressure gradient into the interstitium, across the capillary wall, and into the plasma. Some CO_2 will dissolve in the plasma, and some will dissolve in the erythrocyte.
From our essential knowledge discussion, remember that approximately 10% of the CO_2 will directly dissolve in the plasma, and 90% will diffuse into the red blood cell (RBC). You may ask, what will happen to the 90% that diffuses into the RBC? Well 10% of the 90% of CO_2 that diffuses into the RBC will bind directly to haemoglobin to form carbamino haemoglobin, the remaining 80% combines with H_2O to form H_2CO_3 (carbonic acid) with the help of the enzyme *carbonic anhydrase (CA)*.

$$CO_2 + H_2O \rightleftarrows H_2CO_3$$
$$\uparrow$$
Carbonic anhydrase (present in RBC's and endothelium, not plasma)

H_2CO_3 will spontaneously dissociates into H^+ (hydrogen ion) and HCO_3^- (bicarbonate)

What happens with this formed HCO_3^- and H^+…?

The HCO_3^- :
The HCO_3^- will leave the RBC and remember that 80% of the CO_2 produced by the quadriceps muscle will be transported to the lungs as bicarbonate in the plasma.
When HCO_3^- leaves the cell, Cl^- will enter the cell to maintain electrical neutrality. This is the *chloride shift*, which we have discussed earlier.

The H^+ :
The H^+ will combine with the haemoglobin molecule. The H^+ ions bind to the α-amino and imidazole groups of haemoglobin and alter the allosteric conformation of the haemoglobin, which reduces the affinity of oxygen to haem [1]. Remember that this haemoglobin molecule is saturated with 4 oxygen molecules because it is coming from the lungs.
The H^+ will protonates the histidine residue in the haemoglobin molecule and this will cause stabilization of the T state. The T state of haemoglobin is not favourable for oxygen to be bound to haemoglobin and oxygen will be released for usage by the tissues.

The Haldane effect…[1,2,7]
The increased capacity of deoxygenated haemoglobin to carry CO_2 is referred to as the Haldane effect.

De-oxygenated haemoglobin binds more H^+ than oxyhaemoglobin and de-oxygenated haemoglobin forms carbamino compounds more readily than oxyhaemoglobin.

Let's dissect and explore above statement:

De-oxygenated haemoglobin forms carbamino compounds more readily than oxyhaemoglobin
Explanation:

> The attachment of oxygen to haem reduces the capacity of haemoglobin to carry CO_2. The reason for this is that O_2 increases the ionization of nitrogen groups, which reduces the capacity of the globin chain to carry CO_2 as carbamino compounds. De-oxyhaemoglobin can carry more CO_2 in the form of carbamino compounds, which account for about one third of the arterial venous difference of CO_2 carried in blood.

De-oxygenated haemoglobin binds more H^+ than oxyhaemoglobin
Explanation:

> De-oxyhaemoglobin is more basic (due to the large number of imidazole groups present in the histidine moieties) and therefore has an increased capacity to mop up the H^+ ions produced when carbonic acid dissociates and so has an increased buffering capacity for CO_2.

Consequently, venous blood carries more CO_2 than arterial blood, and CO_2 uptake is facilitated in the tissues and CO_2 release is facilitated in the lungs.

A simplified way to explain the Haldane effect [6]
Let me set the scene:
Imagine a RBC that is returning from the hard working quadriceps muscle and is now arriving in a pulmonary capillary adjacent to an alveolus. Remember that the haemoglobin molecule in this RBC has given off oxygen to the quadriceps muscle. The P_{AO_2} of the alveolus = 90 – 100 mmHg (12 – 13,3 kPa). In the plasma of this pulmonary capillary is HCO_3^-.This HCO_3^- will diffuse into the RBC, and as this happens, Cl^- will diffuse out of the cell (remember that at the quadriceps muscle, HCO_3^- diffused out of the RBC, and Cl^- diffuses into the RBC)
The haemoglobin in this RBC (de-oxyhaemoglobin) got a H^+ attached to it as well as CO_2.
Now that the scene is set, let's see what happens:

1. Oxygen diffuses down its partial pressure gradient from the alveolus into the RBC.
2. As oxygen enters the RBC, it combines with haemoglobin.
3. When O_2 binds to haemoglobin, the H^+ and CO_2 are released from the haemoglobin molecule.
4. What happens to the released H^+?
   a. Well, H^+ will combine with HCO_3^- to form H_2CO_3 (carbonic acid)
   b. H_2CO_3 (carbonic acid) dissociates with the help of CA (carbonic anhydrase) into $CO_2 + H_2O$
   c. The CO_2 formed from the dissociation of H_2CO_3 will diffuse out of the cell and will diffuse down a partial pressure gradient into the alveolus from where it will get exhaled!
5. What happens to the CO_2 that is released from the haemoglobin?
   a. This CO2 will also diffuse out of the cell and will also diffuse down a partial pressure gradient into the alveolus from where it will get exhaled

The Double Bohr effect [1,8]

The Double Bohr effect got to do with the exchange of oxygen and carbon dioxide between the mother and foetus.

Let me set the scene to explain the double Bohr effect:

Think about the mother and fetus and think about the total amount of oxygen that goes from the mother to the fetus. Let's quickly revise some important anatomy that will help us to understand.

Umbilical cord:
Remember that there are 2 umbilical arteries and 1 umbilical vein in the umbilical cord. The umbilical arteries carry de-oxygenated blood from the fetus to the placenta and the umbilical vein carries oxygenated blood from the placenta to the fetus.

Placental structure:
The umbilical arteries branches into the chorionic plate. On the maternal side of the chorionic plate is a pool of blood. The chorionic plate got little extensions that dip into this pool of blood. In these extensions are fetal capillaries, which are tiny extensions of the umbilical vein and umbilical arteries. The mother's uterine arteries also open into the pool of blood, supplying oxygenated blood and the mother's uterine veins drain deoxygenated blood to the mother's lungs. Behind the pool of blood on the mother's side is the thick muscular uterine wall.

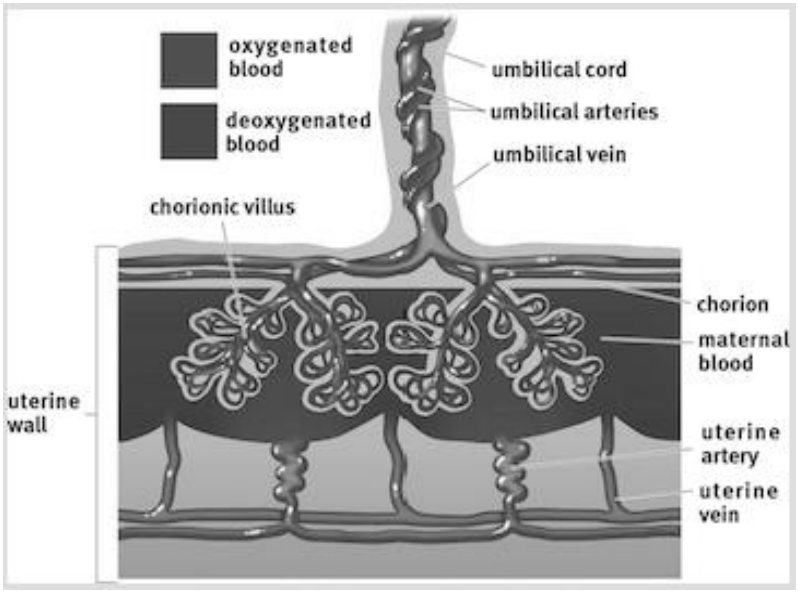

Fig. 6.

Image from:
Google images

Let's look at the oxygen content on the mother's side and the oxygen content on the side of the fetus:

	Po_2	HbA saturation	HbF saturation
Uterine artery (mother)	100 mmHg	98%	
Uterine vein (mother)	40 mmHg	75%	
Umbilical artery (fetus)	18 mmHg		45%
Umbilical vein (fetus)	28 mmHg		70%

Have a look now at fig. 7. Look at the differences between the 4 drawn curves.

- The umbilical artery has a higher carbon dioxide content and lower pH (and higher hydrogen ion concentration) than the umbilical vein.
- The difference in oxygen saturation between the umbilical artery and umbilical vein lines is called the Bohr effect.
- The uterine vein has a higher carbon dioxide content and lower pH (and higher hydrogen ion concentration) than the uterine artery.
- Similarly, the difference in oxygen saturation between the uterine artery and uterine vein is also called the Bohr effect.

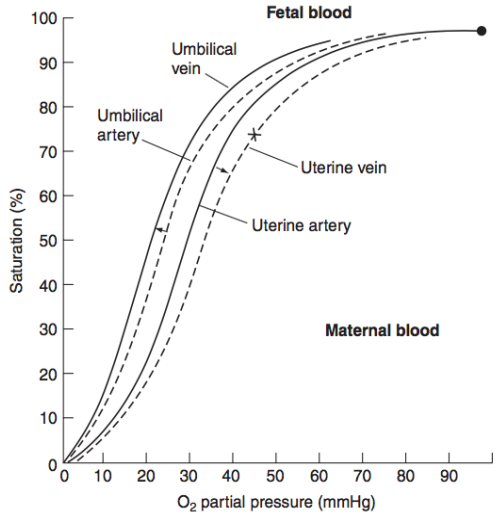

Fig. 7. Transport of oxygen from the mother to the fetus: the double Bohr effect

Image from:
Power I, Kam P. Chapter 3: Respiratory physiology
Principles of Physiology for the Anaesthetist, second edition. Hodder Arnold

Remember from our discussion earlier, the Bohr effect happens when carbon dioxide and hydrogen ions makes oxygen 'fall off' haemoglobin or haemoglobin doesn't bind oxygen well in the presence of carbon dioxide and hydrogen ions.

Let's discuss another obvious difference between the 2 fetal curves of the and the 2 maternal curves.

- The fetal curves (umbilical artery curve and umbilical vein curve) are pushed to the left, this is because the fetus has haemoglobin F with a higher affinity for O_2 compared to haemoglobin A.

Finally, let's look at the Bohr effects:

Bohr effect on the fetal side:

- The Bohr effect takes place when the release of carbon dioxide from the fetal blood inside the chorion enhances the uptake of oxygen. To illustrate this on the diagram, it is the vertical difference between the umbilical artery curve and the umbilical vein curve.

Bohr effect on the maternal side:

- Inside the pool of blood, the carbon dioxide levels are slowly rising, and the Bohr effect causes the release of oxygen molecules from the maternal haemoglobin, which causes a right shift of the curve. Again it can be illustrated on the diagram by the vertical distance between the uterine artery and uterine vein curve.

Because both these Bohr effects are happening in the placenta we call it the double Bohr effect. The double Bohr effect refers to the 4 lines illustrated in the diagram. All of this is happening in the placenta at the same time!

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Anaesthetic Breathing Systems

Prof. Peter Gordon

Dept of Anaesthesia & Perioperative Medicine
University of Cape Town

Anaesthetic breathing systems link the patient to the common gas outlet of the anaesthetic machine, thereby supplying a source of oxygen, anaesthetic gas / vapour, and a means of removing exhaled carbon dioxide. The different breathing systems vary in their ability to eliminate carbon dioxide during spontaneous and intermittent positive pressure ventilation. Anaesthetic machine have a coaxial male 22 mm, female 15 mm conical connector to the breathing systems.

Classification of breathing systems

Classifications by Conway in the UK, and Dripps in the USA, using the terms open, closed, semi-open and semi-closed, differ in definition, are confusing, and are not discussed further.

The best and most comprehensive classification of breathing systems is that developed by South African trained anaesthetist, Dr Don Miller who devised a classification of breathing systems based on their structure and function.

Classification of breathing systems after Miller [1, 2]

Breathing systems are divided into two broad classes depending on whether they absorb carbon dioxide or not.

Further subdivision depends on whether flow in the breathing system is unidirectional or bidirectional.

Bidirectional flow systems are further subdivided into ***afferent*** and ***efferent*** and ***junctional*** reservoir systems. Afferent tubes supply fresh gas from the anaesthetic machine to the patient and require a reservoir in the afferent limb hence the term **afferent reservoir system.** Efferent tubes carry predominantly expired gas from the patient to the exhaust valve. Junctional reservoir systems (such as the Magill B or C have a reservoir bag close to the junction of the afferent and efferent tubes.

The individual systems in each subgroup have similar fresh gas flow requirements and performance characteristics.

Classification of breathing systems after Miller [1, 2]

1. Systems with absorption of carbon dioxide

(i) ***Unidirectional flow*** **– circle system (Kuhn, Sword (1930)**

(ii) ***Bidirectional flow*** **– To-and-fro cannister (Waters 1924)**

2. Systems without absorption of carbon dioxide

(i) ***Unidirectional flow***
- **(a) Non rebreathing valves (Rubin, Laerdal, Fink, Ambu)**
- **(b) Circle system (Eger and Ethans)**

(ii) ***Bidirectional flow***
- **(a) Simple afferent reservoir (Magill, Lack, Miller)**
- **(b) Enclosed afferent reservoir (Miller & Miller 1988)**
- **(c) Junctional reservoir (Mapleson B and C)**
- **(d) Efferent reservoir** (Bain, Mapleson D, E, F)

The following systems for providing inhalational anaesthesia will be discussed.

Insufflation

The blowing of anaesthetic gases across a patient's face using a mask is sometimes used for induction of anaesthesia, particularly in paediatric practice in patients resisting the placement of a mask on their face. The inspired concentration from this technique is unknown.

Draw-over anaesthesia systems

Simple portable, draw over systems have found use in resource strapped hospitals where gas supplies are unreliable, and in military conflict zones such as in the Falklands war and in Iraq. [1] In draw-over systems air or oxygen enriched air is drawn through a low resistance vaporizer by the patient's inspiratory effort. An AMBU type valve providing one way flow of gases is necessary to prevent rebreathing. Examples of suitable vaporisers are the EMO ether vaporiser, and the Tri-service apparatus using in series halothane and trichloroethylene PAC vaporisers and the Ohmeda Universal Portable Anaesthetic Complete Apparatus (U-PAC) used by US forces in Iraq.

Problems include limited control of anaesthetic concentration and theatre pollution.

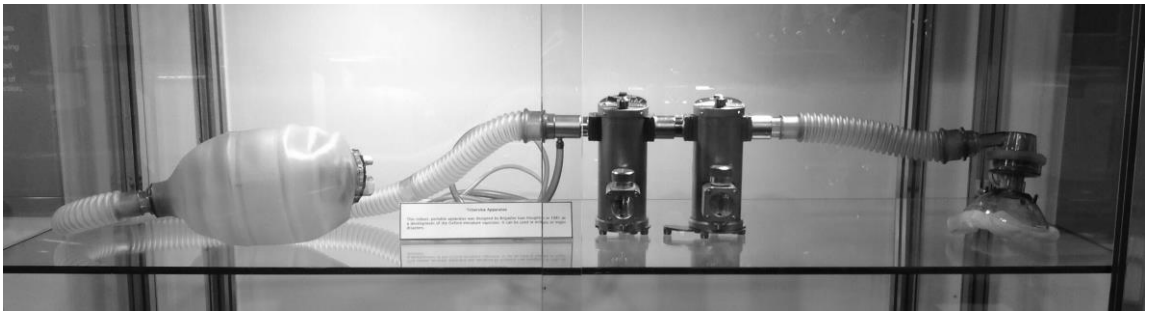

Fig. 1 Triservice anaesthetic apparatus as used in the Falklands War.

Image from
Out of our comfort zone: Pain relief in a crisis, display at the AAGBI History of Anaesthesia Museum

Mapleson Breathing Systems [3]

In 1954 Mapleson described and analysed the performance characteristics of five different semi-closed anaesthetic systems that are categorized from A-E. A sixth system, the Mapleson F was added later. (Fig. 2)

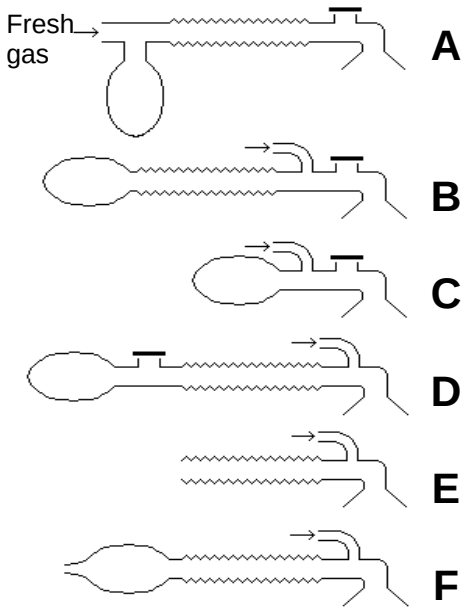

Fig. 2 Mapleson classification of breathing systems

Mapleson A (Magill system)
Designed by Ivor Magill in 1928 this afferent reservoir system was widely used, and is still used today particularly in rural hospitals. It consists of a 3-way T-tube connected to the fresh gas outlet, a breathing bag, a reservoir tube connecting to the patient, and a adjustable spring-loaded expiratory valve at the patient end. It is the most efficient Mapleson breathing system for spontaneous ventilation because it **conserves exhaled dead space gas** and **vents exhaled alveolar gas** provided fresh gas flows of 70 ml/kg are utilised. It is inefficient for controlled ventilation requiring high gas flows (2-3 x minute volume), to prevent rebreathing.
The system is also difficult to scavenge. A co-axial version was designed by Lack in 1976.

Mapleson B and C breathing systems are classified as junctional reservoir systems. Mapleson B systems are obsolete. Mapleson C systems are not used for anaesthesia but are still used in some hospitals for resuscitation and for short-term transport.

Mapleson D
This system is inefficient for spontaneous ventilation because unless gas flows are very high, exhaled gas enters the reservoir bag together with fresh gas. It is efficient for IPPV at a flow rate of fresh gas of 70 ml/kg/min because exhaled dead space gas passes into the reservoir bag together with fresh gas so that the reservoir bag is full by the time that alveolar gas reaches the bag. Alveolar gas is thus vented via the expiratory valve.

The **Bain circuit** (1972) is a popular co-axial form of the Mapleson D that allows easy control of the expiratory valve, and scavenging. Another advantage is that because the fresh gas flow is delivered at the patient end, the tubing can be longer than the standard Magill system without increasing dead space and can therefore be used to provide anaesthesia from a safe distance for MRI.
Disconnection, kinking or leaks of the inner gas supply tube can result in significant breathing of exhaled gas.
The following checks should be performed before using a Bain circuit: [4]

- **Visual inspection** of the inner and outer tube looking for leaks or disconnection of inner tube.
- **Occlusion test** (described by Foex and Crampton-Smith in 1977). After connecting Bain circuit to the common gas outlet, switch O_2 flow to 2 $Lmin^{-1}$ and then occlude the inner tube with the plunger from a 2ml syringe. If there is no leak the flow meter bobbin will drop slightly due to increased back pressure. On release it will return to its original position.
- **Ghani's test** (1984) – a modification of the occlusion test: after connecting the Bain circuit to the common gas outlet of the anaesthetic machine, switch on flow of oxygen at 2 $Lmin^{-1}$, then occlude the inner tube with the tip of a plunger of a 3 ml syringe. On releasing the plunger tip a hissing sound lasting 2-3 seconds should occur due to release of pressure in the inner tube. This will not occur if there is a hole in the inner tube.
- **Pethick's oxygen flush test** – After connecting the Bain circuit to the common gas outlet, fill the reservoir bag with oxygen and then flush the circuit using the oxygen flush button. If there is no leak then the reservoir bag will collapse due to the Venturi effect.

Mapleson E (Ayre's T piece)
Dr Phillip Ayre designed this low resistance breathing system for use in paediatric anaesthesia in 1937. A fresh gas flow of 2-3x minute volume is required to prevent rebreathing. To prevent dilution of anaesthetic gases with room air, the volume of the efferent reservoir limb should exceed tidal volume.
Ventilation could be achieved by intermittent occlusion of the reservoir limb outlet. Disadvantages included difficulties in scavenging and humidifying gases. The Cape Town and other breathing systems were developed to reduce the dead space when anaesthetising a child using a mask with the Ayre's T piece.

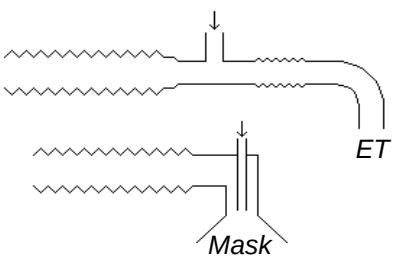

Fig. 3 Top – Ayres T-piece with endotracheal tube and Cape Town breathing system that reduced dead space

Mapleson F (Jackson Rees - 1950**)**
Jackson Rees modified the Mapleson E by adding an open-ended 500 ml bag to the expiratory limb allowing easier manual ventilation and the ability to monitor respiration by observing movements of the bag. Suggested FGF's of 23 x minute volume for spontaneous ventilation and 200 ml / kg for IPPV were recommended.

The **Humphrey ADE system**, designed by Durban anaesthetist and physiologist, David Humphrey in 1981, allows users to choose between using the system in the A, D or E mode and is suitable for use in paediatric, adult and veterinary anaesthesia. [3] Later modification added a soda lime canister.

Systems with carbon dioxide absorption

The idea of using substances to absorb carbon dioxide in breathing systems was known by the early anaesthetists, including Englishman, Dr John Snow. Ralph Waters in Wisconsin popularized the use of soda lime to absorb CO_2 in his Waters to-and-fro canister in 1924. (Waters became the world's first Professor of Anaesthesia). The canister provided excellent humidification and warming of gases, reduced the cost and risk of explosion with expensive gases combustible gases such as cyclopropane. The apparatus was heavy and bulky, and if the canister was not filled with absorbent would allow channeling to occur. The latter problem was solved by Johannesburg anaesthetist Hymie Samson who designed a see through casing for the absorbent that allowed visual inspection of the absorbent and the use of indicator dyes to demonstrate when the soda lime was no longer absorbing CO_2.

Fig. 4 Waters to-and-fro canister modified by Samson

Circle Breathing System
The circle breathing system, using soda lime to absorb carbon dioxide is the most popular breathing system currently in use. The earliest system of this type was developed by Carl Gauss in 1925 and manufactured by Drägerwerk of Lübeck. Germany. American Brian Sword popularised the circle system in the English-speaking world in 1930.

It consists of seven components: (1) A fresh gas inlet from the common gas outlet of the anaesthetic machine, (2) inspiratory and expiratory corrugated tubing, (3) inspiratory and expiratory valves, (4) a canister containing carbon dioxide absorbent, (5) a reservoir bag, (6) an adjustable pressure limiting (APL) valve, and (7) a Y-piece connector. Modern circle systems also have a bag/ventilator switch and a ventilator that is usually either a piston driven ventilator (Dräger) or an ascending bellows.

For optimal function the following configuration is most satisfactory:

- The fresh gas inlet must be placed between the absorber and the inspiratory valve.
- The APL valve should be situated between the expiratory valve and the absorber
- The bag/ventilator switch should be in the expiratory limb so that during IPPV exhaled gas will be vented through the APL valve.
- For optimal function the unidirectional valves should be close to the patient to prevent backflow into the inspiratory limb in the event of a leak in the circuit. They are however not placed in the Y-piece as in this position they would often be difficult to observe during surgery.

Valve malfunction can occur due to water condensation on the expiratory valve resulting in partial obstruction to expiration and rebreathing. Valve malfunction can also occur due to wearing of the valve seat.

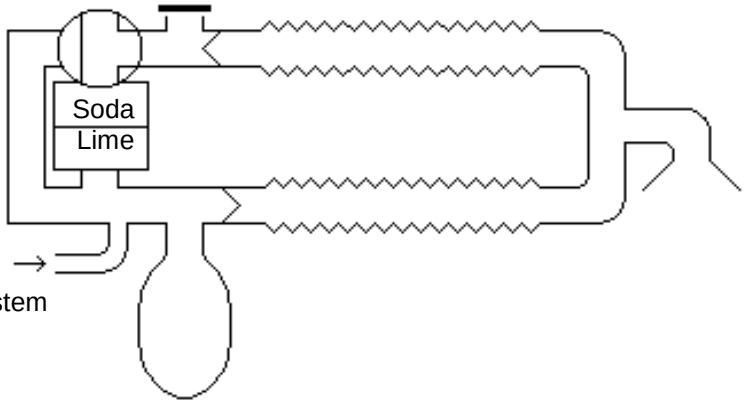

Fig. 5 The circle breathing system

Advantages include cost savings when using low gas flows, humidification and warming of gases, the ability to easily switch between spontaneous and controlled ventilation, decreased theatre pollution, and a reduction in the risk of fires and explosions when using inflammable agents such as cyclopropane and ether.

Disadvantages include the complexity of the system with multiple components, which can lead to misconnections, disconnections, and leaks. Valves stuck in the open position can cause rebreathing, and sticking of the expiratory valve can result in breath stacking and tension pneumothorax. The increased resistance to breathing will lead to increased work of breathing especially in paediatrics. Resistance can be reduced by using circulation fans. Cross infection between patients is another potential problem that can be diminished by using appropriate filters, or abolished by using disposable circuits.

Soda-lime

In these systems, the expired carbon dioxide is removed by absorbing exhaled gas using an absorbing compound (either Soda-lime or Amsorb) contained in a canister. The remaining expired gas is then free to be inspired again without accumulation of carbon dioxide occurring.

Soda lime is a mixture of 94% calcium hydroxide, 5% sodium hydroxide and 1% potassium hydroxide, silicates for binding (<1%) a pH sensitive indicator dye, and a water content of 14 – 19%. The calcium hydroxide provides the main capacity for carbon dioxide removal by soda lime, the potassium and sodium hydroxide being added to accelerate the rate of absorption. Amsorb contains no potassium hydroxide. The sodium hydroxide and water required are regenerated. Carbon dioxide absorption occurs by the following chemical reactions:

$$H_2O + CO_2 \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

$$NaOH\ (\text{or } KOH) + H_2CO_3 \rightleftharpoons NaHCO_3\ (\text{or } KHCO_3) + H_2O\ (+ \text{heat})$$ *[fast reaction]*

$$2NaHCO_3\ (\text{or } KHCO_3) + Ca(OH)_2 \rightleftharpoons 2NaOH\ (\text{or } KOH) + CaCO_3 + H_2O$$ *[slow reaction]*

Amsorb contains calcium hydroxide and calcium chloride with substances to increase hardness.

Baralyme 20% barium hydroxide is no longer used because of its propensity to produce CO with desflurane, sevoflurane and isoflurane.

Soda lime granules are usually between 4-8 mesh in size (will fit between a mesh of 4 – 8 strands / $inch^2$). If granules are too small resistance to breathing increases and 'dust' may be inhaled. If

granules are too large channelling will occur with inefficiency of CO_2 absorption. The volume of the space between granules should equal the volume of the granules. Double canisters are often used with a baffle to direct gas flow centrally to reduce channelling. Absorbers have a trap at the base to collect water and dust.

Problems with chemicals used in absorbers to remove CO_2

- Production of carbon monoxide. This particularly likely when absorbents are allowed to become desiccated, as may happen when gases are not switched off after use. Dangerous levels of carboxyhaemoglobin of up to 30% have been recorded. Baralyme was worse than other agents and was withdrawn from use in the US in 2004.
- Absorbents have been shown to absorb volatile agents and release them later leading to slower than expected induction, and emergence from anaesthesia.
- Compound A is a by-product of absorption of sevoflurane by absorbents. Although Compound A is nephrotoxic in some animals this is thought not to be a problem in humans.
- Historically, trichloroethylene (trilene) was shown to cause significant neurotoxicity in humans when used with soda lime.

There are two indicators in common usage - ethyl violet which turns from white to purple and the other changing from pink to white upon exhaustion, which may result in confusion.

Advantages of rebreathing systems

- Economy of anaesthetic consumption.
- Warming and humidification of the inspired gases.
- Reduced atmospheric pollution.

Ideal properties of a breathing system/circuit

- Ability to deliver a targeted anaesthetic concentration
- Suitable for spontaneous and assisted ventilation
- Minimise gas flow
- Remove carbon dioxide
- Low resistance
- Efficient (save volatile agent)
- Humidify and warm gases
- Easy to use and lightweight
- Allow scavenging of anaesthetic gases

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Anaesthesia Vaporisers

Dr Rob Nieuwveld

Dept. of Anaesthesia & Perioperative Medicine
University of Cape Town
Red Cross War Memorial Children's Hospital

INTRODUCTION

A volatile anaesthetic agent has been part of anaesthesia practice since the first demonstration of anaesthesia by William T G Morton (1846) and remains the dominant method of maintaining general anaesthesia. The inherent advantage of simply switching off to remove the agent allows for rapid reversal and safety (only recently achieved with intravenous agents agents).

The development of devices for the vaporisation and accurate delivery of volatile agents occurred hand-in hand with the search for better agents (Ether to Desflurane).

Devices for the delivery of volatile anaesthetic agents, from the simple ether sponge of Morton to the latest Tec 6 and Aladin® cassettes are designed using basic physical principles.

BASIC PHYSICS

Gases and Vapours

A **gas** is a substance above its *critical temperature* whilst a **vapour** refers to the gaseous state of a substance below the *critical temperature*.

Strictly speaking, Nitrous Oxide (N_2O), Carbon Dioxide (CO_2) and Cyclopropane (C_3H_6) (all delivered in "gas" cylinders) are vapours; but commonly referred to as gases as they are in the gaseous phase at room temperature and ambient pressure, but may be a liquid in the cylinder under pressure.

Critical Temperature and Critical Pressure

The **critical temperature** of a substance is the maximum temperature above which it cannot be liquefied, irrespective of the pressure exerted; and the **critical pressure** is the pressure required to liquefy it (i.e. the vapour pressure) at the critical temperature.

Below the critical temperature, a substance may exist as a vapour, a liquid or both; depending on the temperature and pressure; as illustrated below.

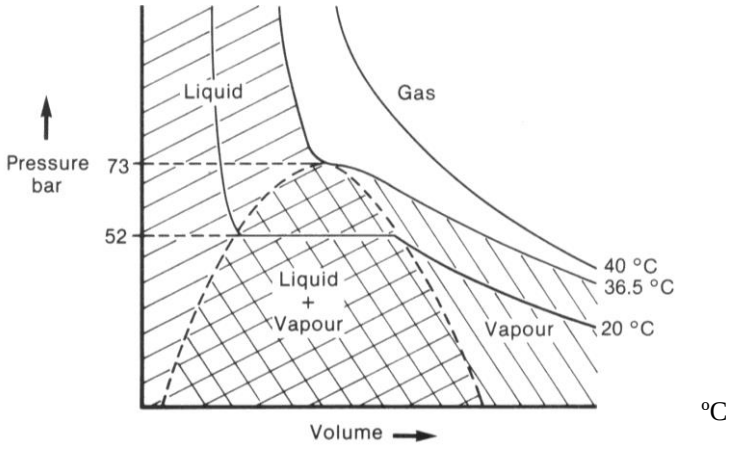


Fig 1 - Isotherms for N_2O. Critical Temperature for N_2O is 36,5

Illustration from:
GD Parbrook, PD Davis, EO Parbrook.
Basic Physics and Measurement in Anaesthesia.
London: William Heinemann Medical Books; 1982.

Substance	Critical Temperature °C	Critical Pressure Bar = 100 kPa
O_2	-119	49,7
N_2O	36,5	73,0
CO_2	31,2	73,0
Xe	16,6	58,4
H_2O	374	217,7

Table 1 - Physical properties of some gases

Vapour Pressure

In the range of pressures and temperatures in which a substance may exist in both liquid and gaseous forms, there is a constant flux of molecules between these two phases. Molecules with high kinetic energy will overcome the tight inter-molecular forces of the liquid phase and enter the gaseous phase, i.e. evaporation. Molecules in the gaseous phase have high kinetic energy and exert a pressure if confined in a closed container, the **vapour pressure**. At equilibrium (i.e. constant temperature and volume) this is the **saturated vapour pressure** (SVP) at that temperature.

SVP is *dependent on temperature* and *independent of the ambient pressure*.

If SVP equals ambient pressure, the substance will rapidly vaporise and "boil". The temperature at which this occurs is the **boiling point.** The boiling point is thus *dependent on ambient pressure* and will decrease with decreasing pressure (e.g. high altitude).

The closer the boiling point to room temperature, the more volatile the substance.

Agent	Boiling point @ SL °C	SVP @ 20 °C kPa	Blood / Gas partition coefficient @ 20 °C	MAC
Halothane	50,2	32,4	3,6	0,75
Enflurane	56,5	23,3	1,9	1,7
Isoflurane	48,5	31,7	1,4	1,2
Sevoflurane	58,5	21,3	0,6	2
Desflurane	23,5	88,5	0,4	6
Methoxyflurane	104,8	3	12	0,16

Table 2 - Properties of modern anaesthetic agents

Latent Heat of Vaporisation

Vaporisation results in energetic molecules leaving the liquid phase, resulting in a lower kinetic energy state remaining in the liquid. This cools the liquid and *decreases* the saturated vapour pressure.

The amount of heat energy (Joules) needed to prevent this is the **latent heat of vaporisation** - i.e. the amount of heat required to convert a mole of substance from the liquid to the gaseous phase without a change in temperature. The latent heat of vaporisation is *dependent on the temperatur*e, decreasing with increasing temperature and is zero at the critical temperature.

Specific Heat Capacity

The amount of heat energy (Joules) required to raise a kilogram of substance by a Kelvin (K = °C), e.g. Water (H_2O) = 4,18 kJ kg^{-1} K^{-1}, or 1 kcal kg^{-1} $°C^{-1}$. The **heat capacity** of an object is the amount of heat required to raise its temperature by 1 °C.

The heat capacity of a vaporiser is important in maintaining a constant temperature to allow a constant saturated vapour pressure. Vaporisers constructed of material with a high specific heat capacity will be more thermostable than those made of a low specific heat capacity.

Thermal Conductivity

The ease with which heat transfers through a substance. This is important in vaporisers to allow ambient heat to flow to the vaporising chamber and maintain a constant temperature.

Glass, as used in the Boyle's bottle, has a higher specific heat than copper, but does not maintain the temperature as well as it has poor thermal conductivity, even with the use of a water bath.

Material	Specific Heat J kg^{-1} K^{-1}	Relative Thermal Conductivity (Glass = 1)
Copper	385	403
Aluminium	897	236
Brass	383	53
Steel	466	25
Glass	840	1
Water	4181	0,6
Air	1012	0,02

Table 3 - Physical properties of materials used in vaporisers

Vapour Concentration

Volume percent vs. partial pressure

Traditionally, vapour concentration is expressed in volume percent (vol. %), i.e. unit volumes of vapour in 100 unit volumes of carrier gas; and modern vaporisers reflect this on the dial. However, clinical effect is **dependent on partial pressure** (kPa or mm 'Hg') of the vapour, **not** the vol. % concentration.

Partial pressure is *independent* of ambient pressure and this assumes importance with vaporisers at altitude and the method used to calibrate them.

The concept of the Minimum Alveolar Concentration (MAC) could be more correctly applied as the Minimum Alveolar Partial Pressure (MAPP).

Dalton's Law of Partial Pressure states that the total pressure a mixture of gases and / or vapours exerts is equal to the sum of the individual pressures that each gas or vapour would exert if it alone occupied that space.

$$\frac{\textbf{Partial Pressure of Vapour}}{\textbf{Total Ambient Pressure}} = \frac{\textbf{Volume Percent}}{\textbf{100}}$$

i.e. **MAC** changes with altitude, **MAPP** does not. An advantage of using the SI unit for Pressure, the Pa, is that the ambient pressure at sea level is ± 100 kPa and vol. % is more or less equivalent to kPa.

Avogadro's Hypothesis

Equal volumes of "ideal gases" at the same temperature and pressure will contain the same number of molecules. One mole of any gas at Standard Temperature and Pressure (STP = 0 °C and 101 kPa) will have 6,02 x 10^{23} molecules (Avogadro's Number) and occupy 22,4 L; or 24 L at 20 °C.

This principle may be used to produce a mixture of gases used to calibrate vaporisers (or the instruments used to calibrate them, e.g. Rayleigh's refractometer).

ANAESTHETIC VAPOUR DELIVERY SYSTEMS

There are essentially three modern methods of delivering anaesthetic agents to a breathing system:

a) Variable bypass vaporisers
b) Gas / vapour blenders
and c) Liquid anaesthetic injectors

A comprehensive classification of anaesthetic vapour delivery devices does not exist. Some of the factors that may be used in a classification are illustrated below.

Method of regulating the output:
- Concentration calibrated
- Flow measurement (e.g. Copper kettle)

Method of Vaporisation:
- Flow-over
- Bubbler
- Injector
- Heated

Temperature compensation:
- Thermo-compensated
- Supplied heat
- Dial correction (e.g. original Dräger Vapor)

Flow resistance:
- Plenum (high resistance)
- Draw-over (low resistance)

Flow stability

Specificity:
- Agent specific
- Multi-agent (e.g. TriTec)

Resistance to back-pressure

Position in the anaesthesia system:
- Vaporiser in circuit (VIC)
- Vaporiser out of circuit (VOC)

a) *VARIABLE BYPASS VAPORISERS*

The basic design is a vaporising chamber which allows gas to become saturated with vapour in equilibrium with the anaesthetic liquid, and a bypass channel, with a means of varying the ratio of flows between them; resulting in a known concentration of anaesthetic vapour in the output.

Regulating the vaporiser output

The volume of gas / vapour that exits the vaporising chamber exceeds that which enters it by the amount of vapour that has been added. This extra volume is determined by the Saturated Vapour Pressure (SVP), which in turn is determined by the temperature and the agent in question.

Isoflurane has a SVP at 20 °C of ± 32 kPa or ± 32 % at sea level (100 kPa), i.e. 32 % of the vaporising chamber output will be isoflurane and 68 % carrier gas. If carrier gas inflow is 100 mL min^{-1}, then the total outflow from the vaporising chamber will be:

$$\textbf{Total output} = \textbf{Inflow} + \left(\frac{\textbf{\% Isoflurane}}{\textbf{\% carrier gas}} \times \textbf{Inflow} \right)$$

(% carrier gas = 100 - % Isoflurane)

$$= 100 + \left(\frac{32}{68} \times 100 \right) = 147 \text{ mL min}^{-1}$$

i.e. 47 mL of Isoflurane vapour has been added to the 100 mL carrier gas, at sea level.

To allow for ambient pressure changes (e.g. altitude), SVP instead of % is used and the formula is:

$$\textbf{Total output} = \textbf{Inflow} + \left(\frac{\textbf{SVP}_{\textbf{anaes agent}}}{\textbf{Ambient Pressure} - \textbf{SVP}_{\textbf{anaes agent}}} \times \textbf{Inflow} \right)$$

$$= 100 + \left(\frac{32 \text{ kPa}}{100 - 32 \text{ kPa}} \times 100 \right) = 147 \text{ mL min}^{-1}$$

The gas emerging from the vaporising chamber is then mixed with the calibrated / controlled carrier gas from the bypass channel to produce a known concentration of anaesthetic vapour.

This is achieved in 2 ways.

1. *Variable bypass vaporisers*

This includes the Boyle's bottle and most modern vaporisers and have the bypass channel incorporated in the unit. The total fresh gas flow is split by a valve / dial between the vaporising chamber and the bypass channel. The flow into the bypass channel far exceeds the flow into the vaporising chamber and the ratio between these, the **"splitting ratio"**, is dependent on the agent, temperature and dial setting.

Concentration-calibrated units deliver a concentration within 20 % (better with modern vaporisers) of the dial setting.

Boyle's bottles and older vaporisers are *uncalibrated* and output will vary with flow, temperature etc.

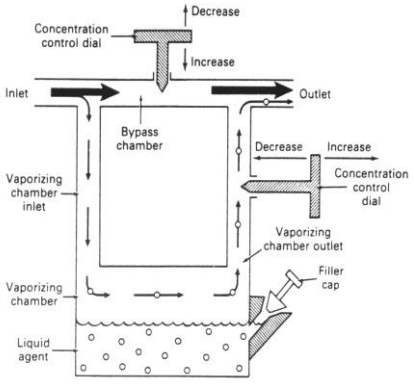


Fig 2 - A generic bypass vaporiser. The control dial may be placed in either the bypass or vaporising channel.

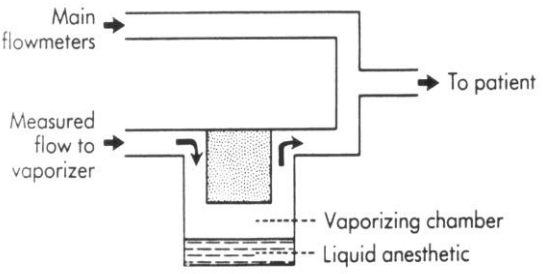


Fig 3 - Diagram of a measured flow vaporiser

Illustration from:
Eisenkraft J. Vaporizers and vaporization of volatile anesthetics.
In: Eisenkraft J (ed). Progress in anesthesiology. Vol 2
San Antonio: Dannemiller Memorial Educational Foundation. 1988.

Illustration from:
Riutort KT, Brockwell RC, Brull ST, Andrews JJ. The anaesthesia workstation and delivery systems.
In: Barash PG (ed). Clinical Anesthesia. 6th edition.
Philadelphia: Wolter Kluwer, Lippincott, Williams & Wilkens. 2009.

2. Measured flow vaporisers

The **"copper kettle"**. A separate O_2 flowmeter delivers a *measured flow* of carrier gas (O_2) through the vaporiser, which is then mixed downstream with the main gas flow which is delivered from the main flowmeters (i.e. there will be 2 *independent* O_2 flowmeters - the vaporiser flowmeter calibrated for low flows). This required tables / calculators and vigilance to deliver the expected concentration. It is probably more feasible with a modern gas / agent monitor, but the method is not used much today.

The formula is:

$$\%\ anaes\ agent = \frac{100\,(\dot{V}_{O2Vap})P_{SVP}}{(\dot{V}_{O2Vap})P_b} + \dot{V}_{Dil}\,(P_b - P_v)$$

$\dot{V}_{O2Vap}$ = Flow of O_2 through vaporiser (ml min^{-1})
P_{SVP} = Saturated vapour pressure of anaesthetic agent (kPa)
P_b = Barometric (ambient) pressure (kPa)
$\dot{V}_{Dil}$ = Flow of diluent gases (ml min^{-1})

Vaporisation methods

To ensure accurate delivery of anaesthetic agent, the gas leaving the vaporisation chamber must be saturated, i.e. the partial pressure of the gas must equal its saturated vapour pressure for that temperature. To achieve this, a large surface area between the gas and liquid phases is required. Surface area may be increased as follows:

Baffles or a spiral track prolongs the exposure time of gas to the liquid, e.g. Boyle's bottle (cowl); Tec vaporisers
Wicks draw liquid by capillary action and increase the surface area. This may be fibre or metal, e.g. Tec 2 (fibre) and Tec 3 - 5 & 7 (metal)
Bubbling gas through the liquid, e.g. Boyle's bottle (plunging the cowl below liquid level); Dräger Vapor and the "copper kettle" (sintered glass or metal)

Many vaporisers use combinations of the above.

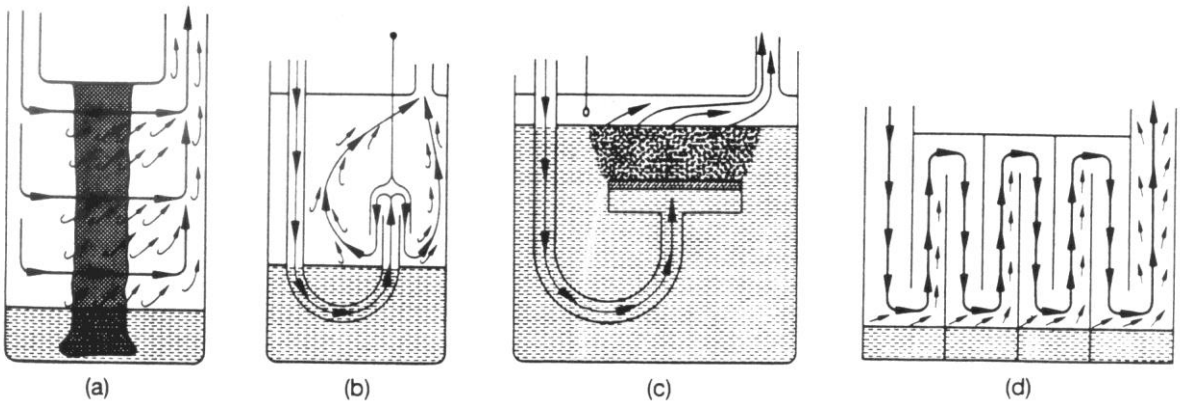


Fig 4 - Methods utilised to ensure saturation of carrier gas by increasing the surface area of the liquid / gas interphase. (a) - Wicks (b) - Cowl (Boyle's bottle) (c) - Bubblers (d) – Baffles

Temperature compensation

As noted previously, saturated vapour pressure is temperature dependent and stability of vaporiser temperature is essential for accurate delivery of anaesthetic agent.

The Latent Heat of Vaporisation tends to cool the vaporiser.

Heat loss may be compensated by:

Maintaining a constant temperature
Altering the "splitting ratio" to allow for the varying temperature

Temperature may be stabilised by using materials with a large heat capacity (hence the reason for the weight of vaporisers) as well as having good thermal conductivity, e.g. copper, aluminium.

The Boyle's bottle was traditionally used with a water bath (high specific heat), but this was only partially successful because glass has poor thermal conductivity.

Maintaining a constant temperature is difficult and calibrated vaporisers alter the "splitting ratio" to compensate for changes in temperature. This is achieved:

Manually, e.g. the original Dräger Vapor (extremely accurate)
Automatically with:

- **A** Bimettalic strips / discs (having different coefficients of linear expansion). These may situated in the vaporising chamber, e.g. Tec 2 or in the bypass channel, e.g. Tec 3 - 5 & 7
- **B** Flexible bellows containing fluid with a high coefficient of expansion, e.g. EMO, Ohio
- **C** Metal rods, e.g. later Dräger Vapor models

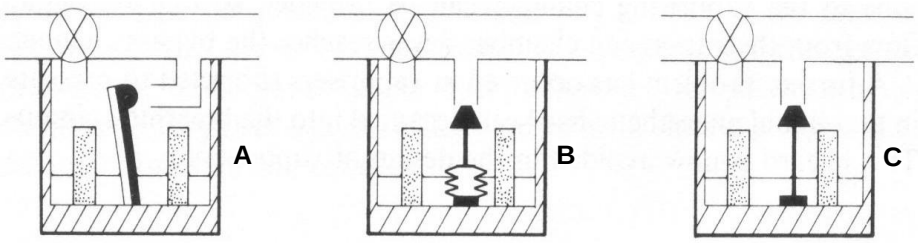


Fig 5 - Methods used to compensate for temperature

Illustration from:
GD Parbrook, PD Davis, EO Parbrook.
Basic Physics and Measurement in Anaesthesia.
London: William Heinemann Medical Books; 1982.

Temperature compensation is effective over a limited range, usually 15 - 30 ºC

Flow resistance

Vaporisers may be of 2 types:

Plenum - This implies a higher pressure in the vaporiser and therefore requires a *constant* positive fresh gas pressure. Most modern vaporisers are of this type and as they have a **high** internal resistance**,** can only be used *before* the breathing system.

Draw-over - Gas may be "drawn-over" the vaporiser, i.e. the patient can breathe through it and all early vaporisers were of this type. It implies a **low** internal resistance and can be placed *within* or *before* the breathing system. If placed within a breathing system, they must be inefficient, i.e. do not achieve high concentrations.
A distinct advantage of this type of vaporiser is that no piped gases are needed and therefore suitable for "field" use, e.g. Tritec apparatus.

Flow stability

Vaporisers tend to be flow dependent. The higher the gas flow, the less time the gas is exposed to the liquid and this tends to decrease the anaesthetic concentration. Further, the "splitting ratio" may be altered at high flows as relatively more gas flows through the bypass channel as it has a lower resistance.

Flow stability is achieved by:

Improving the vaporising chamber efficiency to ensure that saturation is achieved at all clinical flow rates, e.g. wicks, baffles etc.
Using constant flows of carrier gas at higher pressures to overcome resistance and viscosity.
Ensuring that the vaporising chamber and bypass channel have similar volumes and resistance.

Specificity

Modern vaporisers are all agent specific. To ensure that the incorrect agent is not inadvertently put into the vaporiser, agent specific fillers have been designed and are colour-coded.

Multi-agent vaporisers are usually of the "draw-over" type and do not have wicks etc. Often used for "field" work and the dial graduations are changed for the relative agents, e.g. the OMV (Oxford miniature vaporiser)

Resistance to back-pressure

Increasing the pressure in the vaporiser (e.g. with controlled or assisted ventilation) may affect vaporiser output.

Two effects have been described:

1. The "pumping effect" (Hill & Lowe)
   Originally described with the Tec 2 vaporisers. Vaporisers deliver higher concentrations of anaesthetic agents with IPPV than with spontaneous ventilation. The effect is accentuated with an underfilled vaporising chamber; low fresh gas flows; frequent and high pressure ventilation,

and low dial settings.
This is caused by gas being forced into the vaporising chamber via the inlet and outlet tubes from the bypass channel under pressure and then re-expanding when the pressure decreases, resulting in some of the bypass gas (entering via the inlet tube) containing anaesthetic agent and increasing the final concentration.

2. The "pressurising" effect is the expected result when pressure is increased as the result of IPPV. As pressure increases, the saturated vapour pressure becomes proportionally less and anaesthetic concentration drops. The effect is greatest with high fresh gas flows.

The "pumping" effect is more significant than the "pressurising" effect, as it may cause an inadvertent overdose.

These effects may be minimised by:

A high internal resistance of the vaporiser
Having similar volumes for the vaporising chamber and bypass channel
Long inlet and outlet tubes for the vaporising chamber to prevent any bypass gas from reaching the gas / liquid interphase and re-expansion of vaporising chamber gas to reach the bypass
A one-way valve downstream to the vaporiser may reduce the pressure variations.

Other factors affecting vaporiser output

Fresh gas composition

Vaporisers are usually calibrated in 100 % O_2. Changing the composition of the carrier gas may alter anaesthetic agent concentration, especially if the gas is soluble and forms a large proportion of the carrier gas, e.g. 70 % N_2O. On the introduction of N_2O, the solubility results in a large volume of N_2O going into solution in the liquid and the volume leaving the vaporising chamber is thus reduced and the final anaesthetic concentration is lower than expected. The converse is true on cessation of N_2O, when an increase in vaporiser output occurs. These effects are temporary and return to expected values when the liquid is saturated with N_2O or replacement gas and steady state conditions return.

The viscosity of N_2O is greater than Air which is greater than O_2. This may alter the splitting ratio as the high resistance of the vaporising chamber may divert more gas to the bypass channel.

Another reason for a varying output is the difference in density of the gases that may alter the splitting ratio. This may account for the *minor* differences in anaesthetic agent *partial pressure* seen at altitude; as density, but not viscosity, is dependent on ambient pressure and slightly alters the splitting ratio with changing gas composition.

Barometric (ambient) pressure

Vaporisers are calibrated at sea level.

Altering the ambient pressure will significantly alter the output of a vaporiser in vol.% terms; **BUT** the *clinical effect* is solely dependent on the partial pressure, which is independent of ambient pressure. Thus the bypass type of vaporiser needs no compensation at altitude as compared to sea level. Minor differences are seen as a result of changes in the splitting ratio caused by differences in density (pressure dependent) and hence resistance.

The formula is:

$$C^1 \times P_b^{\,1} = C^0 \times P_b^{\,0}$$

$$\text{or} \quad C^1 = \frac{C^0 \times P_b^{\,0}}{P_b^{\,1}}$$

If a calibrated Isofluraneane vaporiser is set to 2 % at sea level (100 kPa) it will deliver ± 2 kPa of Isoflurane vapour.
The same dial setting at an ambient pressure of 65 kPa will deliver:

$$C^1 = 2 \text{ vol.\%} \times (100 \text{ kPa} / 65 \text{ kPa})$$
$$= 3{,}07 \text{ vol.\%}$$

But 3,07 % of 65 kPa = 2 kPa, i.e the partial pressure is the same and hence the clinical effect.

Ideally, the **%** symbol on bypass vaporisers should be **kPa**.

b) *GAS / VAPOUR BLENDERS*

This device does not "split" the carrier gas into a vaporising chamber, but directly delivers the vapour under pressure into the carrier gas stream. Historically, this principle was used in the notorious Pinson "Ether bomb". The modern example of this device is the Tec 6 "vaporiser" for Desflurane.

Because of Desflurane's low boiling point (23,5 ºC) and volatility, it is not suited to the conventional bypass vaporiser operating at room temperature. To deliver predictable concentrations of Desflurane, the operating conditions must be moved away from its boiling point. This could be achieved by refrigeration (in which case a bypass vaporiser could be used) or by heating.

Refrigeration is impractical and not commercially available.

The Tec 6 "vaporiser"

The Tec 6 vaporiser is essentially a "gas cylinder" with a method of maintaining a constant pressure and a delivery valve to allow blending of the carrier gas and Desflurane vapour.

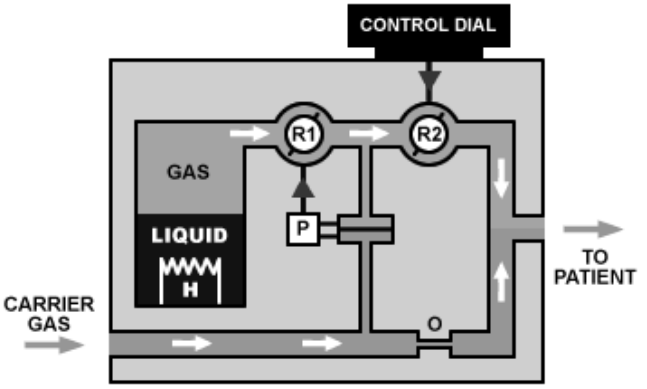


Fig 6 - The Tec 6 "vaporiser" and function

Illustration from:
AnaesthesiaUK. Precision vaporisers [on-line teaching]. 2007.
The Tec 6 desflurane vaporiser.
Available from: http://www.frca.co.uk/images/tec6fun.gif

Liquid Desflurane is heated with servo-controlled heaters (H) to well above its boiling point (39 ºC - at which temperature its SVP is approximately 175 kPa) in a sealed chamber and the Desflurane vapour is blended into the carrier gas.

Carrier gas flow is restricted by an orifice (O) so that the pressure of the carrier gas is proportional to gas flow. This pressure is sensed by a differential pressure transducer (P), which adjusts a resistor (R1) so that the flow of Desflurane out of the vaporising chamber is proportional to the carrier gas flow. This enables the output concentration to be independent of carrier gas flow rate. The control dial adjusts a second resistor (R2), controlling Desflurane vapour output, and thus the concentration.

The Tec 6 is electrically powered and electronically controlled and requires a mains power supply.

As the Tec 6 vaporiser is a vapour blender, the vol.% of anaesthetic agent in the gas output remains constant, irrespective of the ambient pressure, and at altitude will have a lower partial pressure.i.e. The same dial setting will have a *lesser* effect in Johannesburg than in Durban (c.f. the effect with bypass vaporisers) and compensation is required by increasing the dial settings proportionally.

The formula for correction would be:

$$\mathbf{Dial_{Alt} = Dial_{Sl} \times (P_{Sl} / P_{Alt})}$$

(This is the same formula as shown under bypass vaporisers - the principle is the same)

The Desflurane Aladin cassette (Datex-Ohmeda)

This Desflurane vaporiser operates in a dual mode as either a:

- Variable bypass vaporiser - when the Desflurane vapour pressure is at a lower temperature and pressure
- Gas / vapour blender - when the Desflurane vapour reaches a threshold pressure and a valve shuts the inlet to the vaporising chamber

Pressurisation is achieved passively, i.e. there are no heaters (cf. the Tec 6 vaporiser), but there is a fan in the vaporiser to maintain a constant temperature.

c) *DIRECT LIQUID INJECTION OF ANAESTHETIC AGENT*

Manual, direct injection of liquid anaesthetic agent with a syringe and fine needle wasd used for many years for closed circuit anaesthesia. It entailed careful calculations and / or nomograms as well as an exponentially increasing time period for each injection.

Modern *closed circuit* anaesthesia workstations (e.g. Dräger Physioflex and Zeus) use an exponential syringe pump to achieve this, controlled by algorithms and feedback loops from agent analysers.

Siemens developed a "vaporiser" using the technique of directly injecting liquid anaesthetic agent into the carrier gas stream. This device was used on the Siemens Servo 900 series ventilators and later on Kion anaesthesia workstations. The amount injected was controlled by the carrier gas flow and its back pressure. The liquid chamber has an inlet which exposes the pressure of the carrier gas to the liquid and forces this up a tube where it enters the carrier gas stream.

A Desflurane version is not available.

SPECIFIC VAPORISERS

Tec series *- Tec 2 - 5 & 7*

Probably the most widely used vaporisers in RSA and worldwide.

They are of the variable bypass type and are temperature compensated.

Tec 2 (vertical dial) - Uses fibre wicks and baffles to ensure saturation and has a bi-metallic strip in the vaporising chamber for temperature compensation. The splitting ratio is controlled by a valve in the bypass channel at the vaporising chamber inlet. The vaporiser is susceptible to the "pumping effect" as it has a low internal resistance and a large vaporising chamber with short inlet / outlet tubes. It has been used as a draw-over vaporiser. Flow compensation is moderate and at low flows it delivers significantly greater concentrations than dialled and a chart with correction factors should be attached.

Tec 3 (horizontal dial) - Overcame many of the shortcomings of the Tec 2. The temperature compensation is a bimetallic disc in the bypass channel (c.f. Tec 2), the vaporising chamber volume is similar to the bypass channel, longer inlet / outlet tubes and the splitting ratio is controlled at the outlet tube of the vaporising chamber. Wicks in the vaporising chamber are metallic. There is no interlock.

Tec 4 - Essentially the same as Tec 3, but do have an interlock facility that prevents any other Tec 4 (or later) from being switched on if mounted on the correct Selectatec backbar. They may be mounted on older backbars.

Tec 5 and 7 - Essentially are improved versions of the Tec 4 with the new Easy-Fil filling system available on the Tec 7.

The Aladin® cassette *(Datex-Ohmeda AS/5 ADU, Aisys & Aisys CS^2)*

A variable bypass vaporiser used exclusively in advanced Datex-Ohmeda anaesthesia workstations. Agent type is sensed by the position of identification magnets on the Aladin cassette.

Fresh gas enters the Aladin cassette from the upstream flow controls. It is divided into two streams by a fixed restrictor in the bypass unit:

– Bypass Flow: Measured by the bypass flow measurement unit
– Cassette Flow: Measured by the cassette flow measurement unit

Agent concentration is altered by adjusting the cassette *outflow*, with the electronically-controlled flow-control valve from the CPU

The CPU receives input from 6 sources:

– Concentration control dial (set by the anaesthetist)
– Flow measurement unit of the bypass chamber
– Flow measurement unit of the vaporising chamber
– Temperature sensor in the vaporising chamber
– Pressure sensor in the vaporising chamber
– Composition of the carrier gas

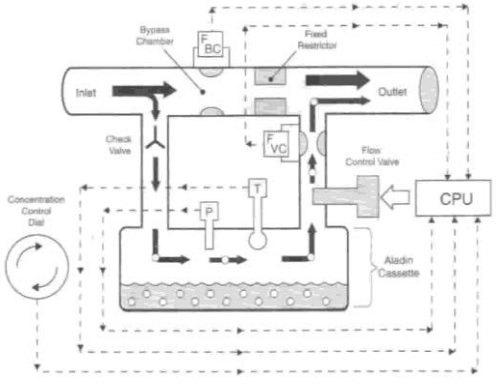


Fig 7 - Function of the Aladin® cassette

Illustration from:
Riutort KT, Brockwell RC, Brull ST, Andrews JJ. The anaesthesia workstation and delivery systems. In: Barash PG (ed). Clinical Anesthesia. 6th edition. Philadelphia: Wolter Kluwer, Lippincott, Williams & Wilkens. 2009.

SAFETY ISSUES

Vaporisers have the potential for serious harm if they inadvertently produce too high a concentration, and numerous safety features have been designed into the modern vaporiser to minimise this.

Hazards include:

Liquid spilling into the bypass channel - This will cause a marked rise in concentration as the "splitting ratio" is in the order of 20 - 50 **:** 1. This usually occurs because of tilting and vaporisers must be securely mounted on the workstation in an upright position. Loose standing vaporisers are dangerous.
The vaporiser should not be able to be turned on if not properly mounted on the correct backbar, and when turned off, the vaporiser chamber should be completely sealed from the bypass channel to prevent spillage during transport. Transport upright!!

Leaks - May result in the inability to ventilate the patient if severe, or cause significant theatre pollution. Most common cause is an incorrectly seated vaporiser on the backbar or the filling device has not been closed properly.

Incorrect agent in the vaporiser - Should not occur if a "keyed" filling system is used, but this is not foolproof. Older pour fillers are dangerous unless only 1 agent is available.
High concentrations will result if an agent of higher volatility (e.g. Halothane or Isoflurane) is placed into the vaporiser of a less volatile agent (e.g. Enflurane or Sevoflurane).

To prevent this, "keyed" fillers have been developed and are available for Methoxyflurane, Halothane, Enflurane and Isoflurane (and Sevoflurane in the USA).
More recently, improved "fillers" have been introduced:
Quik-Fil® for Sevoflurane only. - Owned by Abbot
Easi-Fil® for Tec 7 vaporisers for Halothane, Enflurane and Isoflurane. - Datex-Ohmeda
Saf-T-Fill® for Desflurane. - Baxter

More than 1 agent being delivered - Dangerous and may contaminate the downstream vaporiser.
Modern backbars have interlocks that automatically prevent more than one agent from being delivered. Older backbars have a selector switch to manually choose the vaporiser to be used, but this allowed the non-selected vaporiser to be switched on by mistake and no anaesthetic agent being delivered.
If multiple vaporisers are mounted on a non-interlocked backbar, the most volatile agent should be mounted downstream, i.e. the order would be:

Sevoflurane > Enflurane > Isoflurane > Halothane > Desflurane

Does not prevent delivery of more than one agent, but minimises downstream contamination.

Inadvertent use of a high resistance vaporisers in the breathing circuit - Besides the difficulty of ventilating the patient with the high resistance, these vaporisers are extremely efficient and the anaesthetic agent concentration would rapidly rise to unacceptable levels as the bypass gas contains expired anaesthetic agent.
This is prevented by not permitting 22 mm and 15 mm ISO taper connections to be used and thus preventing them to be mated to a breathing system.
Inefficient draw-over vaporisers may be used in the breathing system and have compatible fittings.

Inappropriate high dial settings - Vaporiser output must be limited to the clinically useful range and this is a function of the blood / gas partition coefficient of the agent (refer to Table 2).
An agent with a high blood / gas partition coefficient (e.g. Halothane) may need a significant amount of "over-pressure" to achieve anaesthesia and the vaporiser allows 7 MAC, Isoflurane 4 MAC, Sevoflurane 4 MAC and Desflurane 3 MAC. The Tec 6 Desflurane vaporiser requires secondary confirmation to exceed 12 % (2 MAC) by depressing the safety catch.

Anaesthetic agent analysers with appropriate alarms are the obvious solution to most of the "overdose" problems highlighted above.

Calibration and service

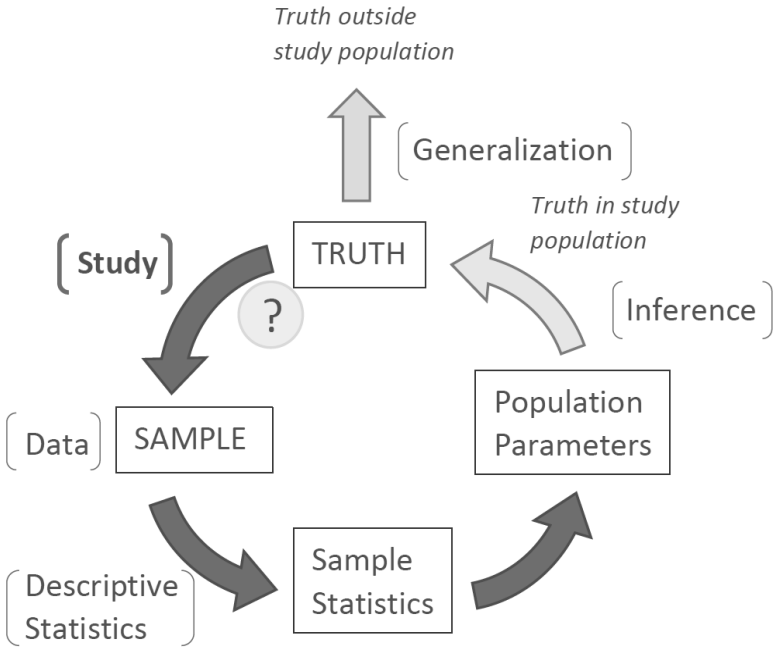
Like any other calibrated device / instrument, vaporisers need to be maintained, serviced and calibrated according to manufacturers' instructions. Halothane vaporisers are more costly in this respect as the preservative in Halothane (thymol blue) leaves a residue requiring more frequent maintenance. The service interval varies, but modern vaporisers have service intervals that may extend from 2 x a year to every 7 years.

An Introduction to Statistical Methods for the FCA 1

Dr Leon du Toit

Dept of Anaesthesia & Perioperative Medicine
University of Cape Town

- Why do we do research? (1)



- What is different in a census? (1)
- Can you explain internal and external validity in terms of this diagram? (2)

? The study question (and available resources) determines the study design.

Six basic study designs:			
Ecological Study	Observational	Retrospective	Occurrence & associations in groups
Case Study / Case Series	Observational	(Usually) Retrospective	Descriptive
Cross-Sectional Study	Observational	Snap Shot*	Descriptive, Analytical, Diagnostic
Case-Control Study	Observational	Retrospective	Analytical (cannot describe occurrence)
Cohort Study	Observational	Prospective	Descriptive & Analytical
Randomised Control Trial	Experimental	Prospective	Interventional & Analytical

* Loss of temporal precedence. The exposure and outcome of interest is measured concurrently. Also true for ecological studies.

- Why does an RCT provide the highest level of evidence? (2)
- Define prospective and retrospective in terms of the outcomes of interest (2)
- What is an ecological fallacy? (1)

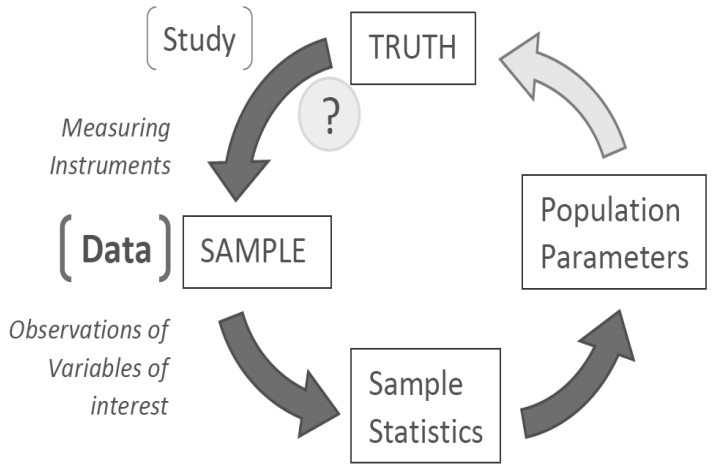
- Define three types of categorical data (3)

- Distinguish between ranked data and discrete data with examples of each (2)

- Give an example of each data type for measuring pain (5)

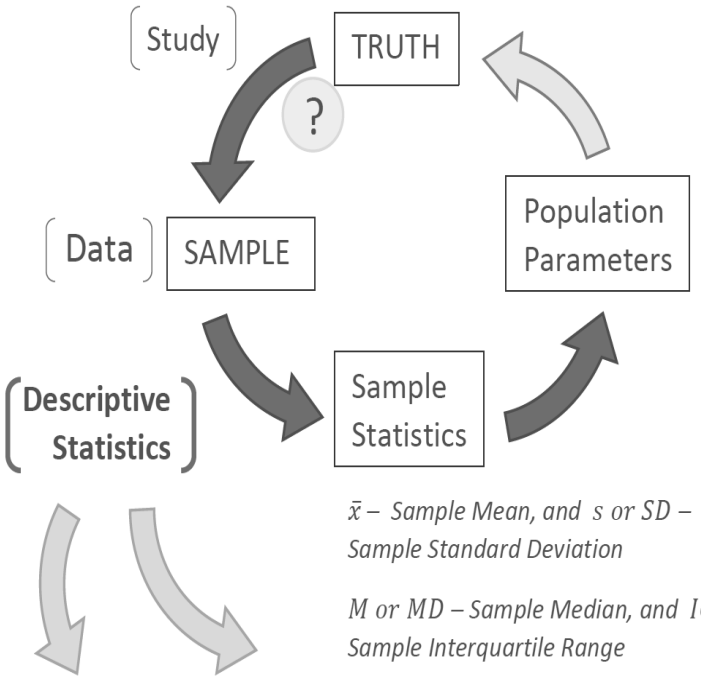
- What is the difference between "wide data format" and "long data format"? (2)

IMPORTANT: these sessions do not discuss sampling methodology which is essential for study validity.



Data types:			
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

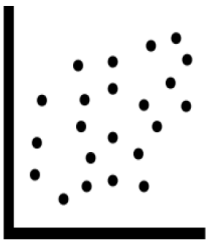
* Our measuring instruments can only measure discretely, however, the data is processed as that of the underlying data type. So even though our thermometer is only accurate to 0.1℃ we still analyse it as continuous data. Then, when we report the results, we stick to the level of accuracy of the measuring instrument.

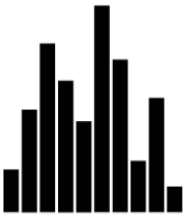


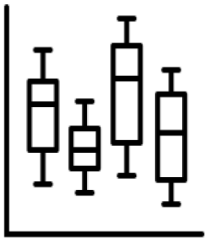
$\bar{x}$ – *Sample Mean, and* s *or* SD – *Sample Standard Deviation*

M *or* MD – *Sample Median, and* IQR *Sample Interquartile Range*

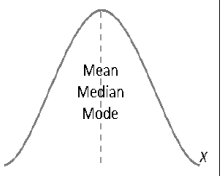
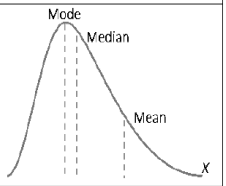
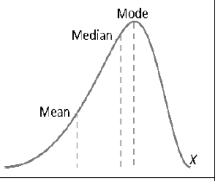
Descriptive Visualisation







Numbers and Tables		
Categorical Data	Count (n)	Proportion $(\%)$
Numerical	Central Tendency $(\bar{x},\ M)$	Dispersion (s, IQR)

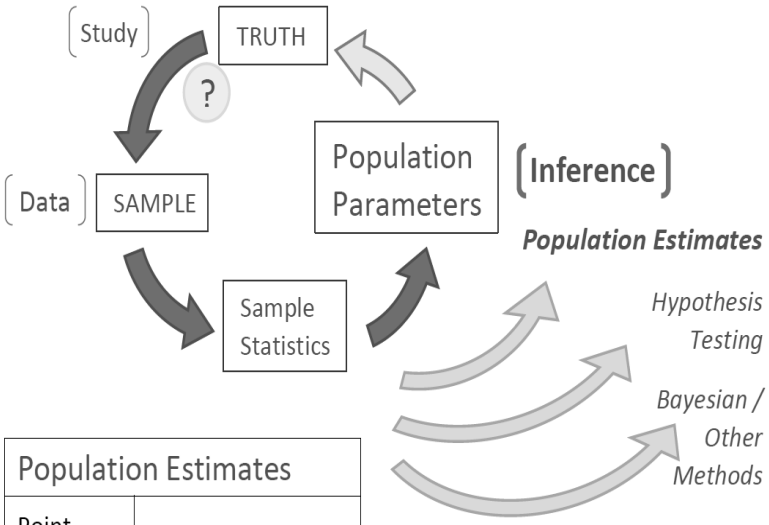
Data Distribution		
Symmetrical	Mean = Median = Mode	
Positively / Right Skewed	Mean > Median > Mode	
Negatively / Left Skewed	Mean < Median < Mode	
Bimodal / Multimodal	≥ 2 Modes	

* Median, Interquartile Range (IQR) is sometimes preferred for smaller datasets (n < 30).

- Name these three simple descriptive visualizations and explain the data source and type for the axes (6)
- Explain the important difference between a histogram and a barchart (2)
- Select the best measures of central tendency and dispersion for these data distributions (3)
- Draw a second symmetrical distribution to show smaller variance (s^2) (1)
- Where are the important outliers in the skewed distributions? (1)
- Draw a bimodal distribution (1)
- Can skewed data be made symmetrical? (2)
- What is the geometric mean? (1)

- What is the Gaussian distribution? (1)
- What are the properties of the normal distribution? (3)
- What is the difference between a normal distribution and the Z-distribution? (1)
- Why do we use degrees of freedom? (1)
- How do you decide if data is normally distributed? (1)

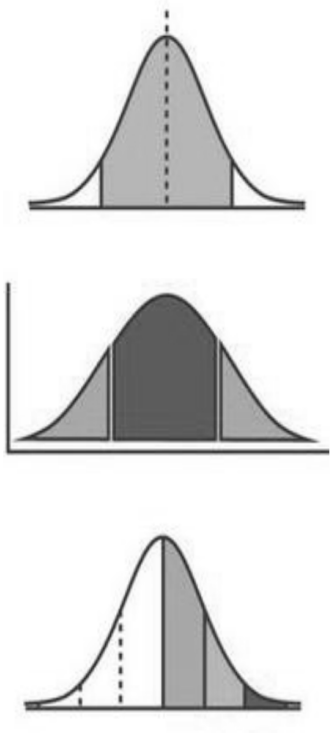
NOTE: The Z-distribution is one of many types of theoretical probability distributions. They refer to mathematical constructs and not actual collected data.



Population Estimates	
Point Estimate	Mean (μ), Median
Range Estimate	95% confidence interval (CI)

Theoretical Probability Distributions

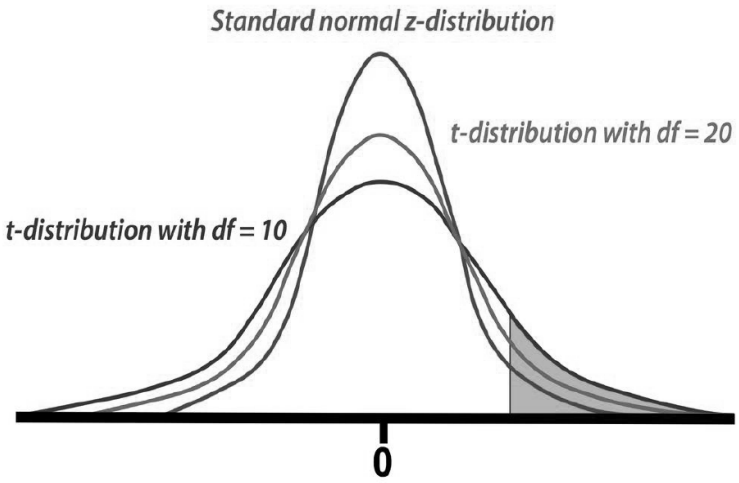
The Normal Distribution



Statistic	Parameter
$\bar{x} = \frac{\sum x}{n}$	$\mu = \frac{\sum x}{N}$
$s = \sqrt{\frac{\sum(x-\bar{x})^2}{n-1}}$	$\sigma = \sqrt{\frac{\sum(x-\mu)^2}{N}}$
The SD is the square root of the variance	

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

The *Shapiro-Wilk Test* was designed to test whether data is normally distributed. It is over-sensitive in most adequately powered studies and therefore rarely relied on.



Sampling distribution of the mean (t)

- Draw a t-distribution with df = 1 on the z-distribution (1)

When we repeatedly sample a point estimate, the distribution of point estimates will resemble a normal distribution regardless of the distribution of the variable in the population. This is referred to as the *Central Limit Theorem.* If we repeat the sampling enough times (> 30 times) the resulting t-distribution is similar to the z-distribution.

- Explain the difference between standard deviation and standard error (4)

The standard deviation of the sampling distribution of the mean is called the standard error of the mean (SEM), or just the standard error (se).

$$SEM = \frac{\sigma}{\sqrt{n}}$$

The standard deviation (σ) tells us about the scatter of data about 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 (for n > 1).

We use the se to calculate the confidence intervals.

- Define 95% confidence intervals (4)

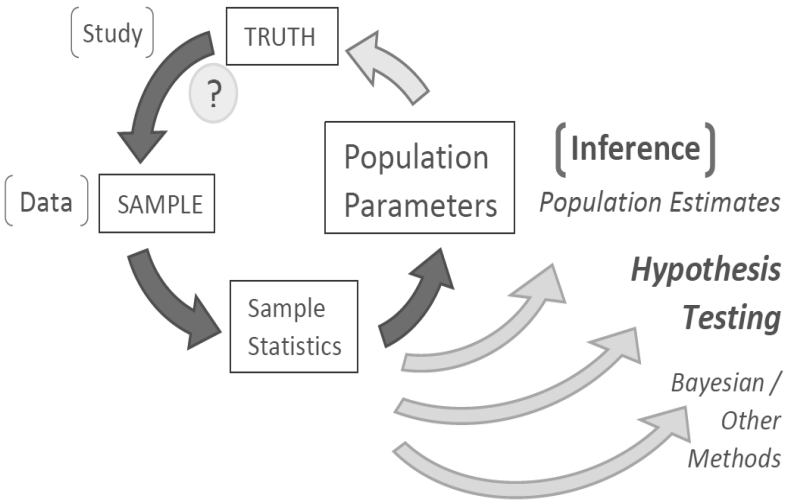
$$95\%\ CI = \bar{x} \pm 1.96 \cdot \frac{s}{\sqrt{n}}$$

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 that is consistent with the sample data. Theoretically, if we were to repeatedly sample the population, 95/100 times the $\bar{x}$ will be included in this range, and by extension it will also contain the μ.

- What is the difference between α and the *p-value*? (2)



- A building burns down because the fire alarm did not get activated. Define the null and alternative hypotheses in this example and use it to explain Type I and Type II errors (4)

Null Hypothesis Significance Testing		
	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
Do no reject H_0	True Negative	Type II error (β)

- Which factors determine the p-value in a study? (3)

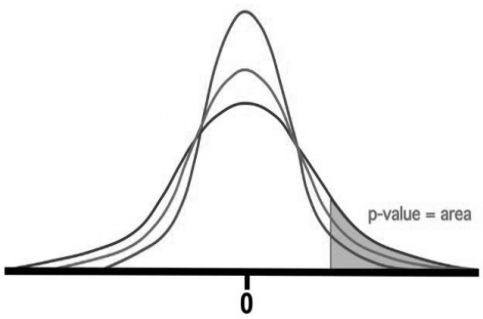
The *level of significance* in a study refers to α, it must be specified *a priori.* It is the probability of rejecting the null hypothesis when it is true. α is typically set at 5%, but this leads to a very high false positive result rate in published literature. Increasingly statisticians are calling for a smaller level of significance.

The *power* of a study is the probability of correctly identifying a difference when it is there (i.e. rejecting the H_0 when it is truly false). *Power* $= 1 - \beta$.

- What is the difference between statistical and clinical significance? (1)

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 H_0 and cannot prove the H_0 or any alternative hypotheses (specific or general).

- How can the 95% confidence interval be used to establish statistical significance? (1)



Guide to choosing the appropriate Hypothesis 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
	Two Independent Proportions		Z-test comparing two proportions
	2×2 and larger $r \times c$ contingency tables of independent samples		Fisher's exact test always valid*, χ^2-test (chi-squared) only if expected values ≥ 5
	2×2 comparison of paired samples		McNemar's test for matched pairs; discordant pairs $(b + c) \geq 10$
	$2 \times k$ 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

- What do the terms parametric and non-parametric refer to? What are the strengths and limitations of each type of test? (4)
- What is the interpretation of the correlation coefficient? (2)
- Explain the post-hoc Bonferroni's correction seen with an ANOVA test (3)

* Fisher's Exact calculation of the *p-value* is computationally arduous; traditionally only used for small expected values where χ^2-test is inaccurate. With a computer Fisher's Exact test is easy and more precise than the χ^2-test.

REGRESSION ANALYSES:

Continuous	Linear
Binary	Logistic
Count	Poisson
Survival	Cox

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Collecting Data
Some thoughts on a framework for designing studies and interpreting the literature

Dr Rowan Duys

Dept of Anaesthesia & Perioperative Medicine
University of Cape Town

Introduction

Making sense of the literature is difficult. There are journals about medicine. There are also journals about anaesthesia in medicine. But what about journals about cardiothoracic anaesthesia in medicine? Or even paediatric cardiothoracic anaesthesia….in Europe…for left handed anaesthetists…who only work on Tuesdays? Reams and reams of *'evidence'* is published and our job as *'evidence-based medicine practitioners'* is to try and sift through it all and decide what is good evidence, what is reliable, what applies to our patients and how we should use it. See? Not easy!

But now, the HPCSA wants us to design and execute our own studies too! The MMed remains a major barrier to completing registrar training in anaesthesia. If researchers with formal research method training, who are supported by teams of research staff and mentorship, still manage to produce poor quality studies, how much harder will it be for busy junior clinicians without the support?

I hope that this brief chapter will deliver a framework that helps you understand the existing literature better, and assists you in navigating some parts of the MMed design and execution phase. It will not be comprehensive, but I hope you find it helpful.

We will focus on:
- A framework for thinking about research design
- Understanding the population in question and thus the generalizability of findings
- Risks to the validity of the findings – systematic and random error

The PICO framework

The PICO framework has helped me understand the papers I read, and design the studies I conceive and execute. I have also used it to define the clinical questions I have in order to assist my searches of the literature.

PICO Framework for clinical questions:

1. Population: define the population of interest
2. Intervention or Exposure: what test, therapy, risk factor, time frame, surgery have the population been exposed to that is of interest
3. Comparator: for studies of therapy, prevention or harm, there will always be a comparison exposure
4. Outcome: What are the relevant consequences of the exposure

I suggest you pick a few of your favourite studies and see if you can apply the framework like this:

Enigma – 2:

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)60893-X/abstract?code=lancet-site

P: 45 or older, known with coronary artery disease, undergoing major non-cardiac surgery
I: Nitrous oxide used in the anaesthetic
C: No nitrous oxide
O: Primary - Composite of death and cardiovascular complications

ASOS

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)30001-1/fulltext

P: 18 or older
I: (Exposure) inpatient surgery
C: observational cohort – so no comparator
O: in-hospital post-operative complications

Various articles and websites expand on this framework, particular as a tool for improving our searching of literature databases. You may find these useful:

https://guides.nyu.edu/c.php?g=276561&p=1847897

https://canberra.libguides.com/c.php?g=599346&p=4149722

But it is also possible to refine your study design process using the PICO framework. And you will have time to experiment with this process during the refresher course proper.

Bias

One of the major tenants of research is the question: Do our results actually represent the truth about a particular population, or do they deviate from the truth? And if they deviate, has this occurred because of random variation between our sample population and the whole population (chance) or because of a deficiency in the research design that enabled systematic differences to occur? These systematic deviations from the truth lead to bias.

There are many different types of bias that may render the results of a study different from the truth, and being aware of some common problems or pitfalls may help you interpret studies better, and design better trials for yourself.

Causes of bias in studies of treatment:

Intervention and control groups may differ at the start e.g.: patients in control group are sicker or older
Intervention and control groups may become different through the course of the study, independent of the experimental treatment e.g.: patients in the intervention group receive additional, effective treatment
Intervention and control groups may differ at the end of the study, independent of the experimental treatment e.g.: more sick patients are lost to follow up from the intervention group and so their data is not included in the analysis

JAMA Evidence, Chapter 5

More specific types of bias include:

1. **Selection Bias** – groups have different prognosis and recruitment, and thus will do better or worse through the study
2. **Detection Bias** – observations of outcomes are not sought as vigilantly as in other groups
3. **Observer Bias** – when the judgement of an observer is required to detect if an event occurred or not, mistakes may happen systematically
4. **Reporting Bias** – (or recall bias) – when memory recall is required of participants to report events (think about whether your memory of your school days accurately represents the entire truth about your experience there)
5. **Response Bias** – when participants who enrol in a trial differ from the population of interest, because they are keen to be involved (think of a survey where those that respond have a vested interest in the outcome)
6. **Publication Bias** – negative studies are less likely to be published than positive studies and so we never learn about the trial where the intervention failed

Reducing Bias

It is possible to employ strategies that systematically reduce the risk of bias. It is worth thinking about them when you analyse a study or when you plan your own.

Reducing bias in studies of therapy and harm:

Source of Bias	Therapy: Strategy for Reducing Bias	Harm: Strategy for Reducing Bias
Differences Observed at the Start of the Study		
Treatment and control patients differ in prognosis	Randomization	Statistical adjustment for prognostic factors in the analysis of data
	Randomization with stratification	Matching Differences
Differences That Arise as the Study Proceeds		
Placebo effects	Blinding of patients	Choice of outcomes (such as mortality) less subject to placebo effects
Cointervention	Blinding of caregivers	Documentation of treatment differences and statistical adjustment
Bias in assessment of outcome	Blinding of assessors of outcome	Choice of outcomes (such as mortality) less subject to observer bias
Differences at the Completion of the Study		
Loss to follow-up	Ensuring complete follow-up	Ensuring complete follow- up
Stopping study early because of large effect	Completing study as initially planned	
Omitting patients who did not receive assigned treatment	Adhering to intention-to-treat principle and including all patients in the arm to which they are randomized	

JAMA Evidence, Chapter 5

Sample vs Population

A sample is a group taken from a population. The population of interest may be all the humans on the continent that will undergo surgery; or, all the cells in the pancreas of a lab rat. Populations are defined by their characteristics, and not by their geography. The challenge for the researcher is to ensure that the sample that is studied, truly represents the population of interest.

A risk with research is that data will be collected from so few patients that any findings that differentiate groups are attributable to chance. For example, a study that tests a new regional technique for knee surgery on 10 of the first 20 patients that come through the theatre doors, may display a benefit of the new technique. But when the study is continued to 100 patients or a 1000 patients, it becomes clear that the benefit found in the initial sample occurred purely because of random variation in outcomes. Put another way: if you flip a perfectly balanced coin and it lands tails-up twice, you might infer that coins always land tails-up. It would require you to flip the coin many more times to be able to confidently state that your coin is balanced and lands tails-up 50% of the time.

Too often in novice researcher studies (I've made the same mistake many more times than I should've), we choose a convenience sample (e.g. how many patients can I recruit in a month), and

end with results that are not statistically significant, and, therefore of limited value. This is a waste of your time, and may put patients at unnecessary risk.

The process of determining the size of sample required to confidently detect a treatment effect, is known as a "power analysis". Various formulae can be used to estimate an appropriate sample; and that's just what it will be, an estimate. I could explain the various formulae to you, but I'd have to kill you….Actually, if it's not already clear, power analysis sits right at the edge of my understanding, and so I get help from a statistician…one day maybe, sigh.

However, before a power analysis and sample size calculation can be performed, it will be necessary to determine the following:

1. The effect size of interest: what size change in outcome will be of clinical interest
2. The variation in the population: what is the standard deviation of the outcome of interest in the population. This is usually determined from previous studies in similar populations or from a pilot study
3. Power: this is the probability that you will be able to detect a significant difference and is arbitrarily set at a certain percentage, usually 80%, but often higher.
4. Significance level: usually set, again arbitrarily, at 0,05
5. Hypothesis: the proposed effect of the intervention or exposure

So when you're designing a study, find the information for the 5 points above, and then approach an expert.

Pragmatic vs Focused trials

The debate around the need for large trials in anaesthesia rages. It is useful for the trainee anaesthetist, evidence-based medicine practitioner, and novice researcher to understand some of the issues at play. However, I'm not sure if it's particularly applicable to the exam candidate.

Traditional tightly controlled RCT's attempt to answer a specific question about a particular population. Your therapy for ischaemic heart disease is more likely to have an effect in a group of high risk individuals with IHD, than in the population at large where the risk of IHD is diluted. And thus many early stage trials did just that: focused on an at-risk population to prove efficacy of a new intervention. However, smaller focused trials to prove *efficacy* have limited generalizability to the greater population. If the patient we have in front of us is similar to the patients studied in the trial, it may be useful information. But it would be inappropriate to apply the new treatment widely.

Large pragmatic trials attempt to prove real-world *effectiveness* testing the effect of simple interventions on simple but important outcomes, such as death or severe complications, when applied widely across a heterogeneous population. This is particularly important in anaesthesia where advances in practice safety have made mortality and morbidity rare. Very large sample sizes are thus required to demonstrate marginal gains in outcomes.

The flip side of the argument for large pragmatic trials is that your patient, is an individual, and does have characteristics that differentiate them from the population. Take the example of a patient diagnosed with significant ischaemic heart disease just before they require major surgery. You may suppose that they would benefit from initiating an appropriate dose of beta-blocker pre-operatively. However, POISE-1 (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(08)60601-7/fulltext), a large pragmatic trial, demonstrated that a high dose of pre-operative Beta blockers generally causes harm when given to all patients with atherosclerosis. So now what do you do?

Conclusion

I hope that this text has explained a slightly random selection of statistical and study design concepts in a way that is helpful. These are the concepts that have changed the way I interpret the literature and have attempted to design trials. If any of the information is confusing or false, I apologise. Stats and research are difficult, and so is interpreting the literature, but it's a necessary part of being a safe evidence-based practitioner and should thus be a life-long project. Good luck!

References

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Testing Data

Prof. MFM James

Emeritus Professor
Dept of Anaesthesia & Perioperative Medicine
University of Cape Town

The Problems of Testing

Unfortunately, biological testing poses a number of problems regarding the accuracy and reliability of the tests that we perform. There is significant biological variation from one patient to another, the instruments we use are of varying accuracy and the skill and experience of the observer also contribute to varying degrees of accuracy. In addition the relationship between the observer to the subject may impact the result (for example "white coat" hypertension), the conditions under which the measurement is made may significantly alter the value (for example preoperative blood pressure measurement) and in addition to these factors there is the natural subject variation in that an individual's given level of a certain value fluctuates on daily, weekly or monthly cycles.

The problem with testing is that it only gives an indication of the presence or absence of a test result whereas the actual event is whether or not the patient has the disease. All tests are flawed in that they all carry a risk of false positives and false negatives and only really give us probabilities and not absolute values. It is particularly important to understand that false positives on screening tests are particularly likely when examining for an event that is very rare (for example, there is no point screening the population for malignant hyperpyrexia).

In considering the value of any given test, the concepts of accuracy and precision must be borne in mind. A test that is fairly accurate may have a degree of scatter but, on average, cluster around the true result, while a test that has only precision may have values that are closely related to each other but may not be very accurate. What we really want is a test that has both accuracy and precision and methods of ascertaining the value of a test in these terms.

All tests used for diagnostic and screening purposes must, in the final analysis, give an absolute in terms of a yes or no answer. The problem lies in defining the choice of an endpoint that is reasonably discriminatory between healthy and diseased subjects.

Determining Effectiveness

The issue of effectiveness is a matter of determining the proportion of patients with a positive test that actually have the disease. This can be expressed in terms of how good the test is at finding every case with the disease, which is called sensitivity and how good the test is at correctly excluding those who do not have the disease, which is referred to as specificity. This can be expressed in terms of a 2 X 2 table (*table 1*).

	Disease Present (D+)	Disease Absent (D-)
Test Positive (T+)	True Positive	False Positive
Test Negative (T-)	False Negative	True Negative

Table 1. A 2 X 2 table showing the relationship between the actual presence of disease and the results of any given test.

The proportion of patients who are disease positive and test positive, together with those who are disease negative but test positive (the sum of the Disease Present column) is called the sensitivity and is expressed mathematically as follows:

$$Sensitivity = \frac{Number\ who\ are\ disease\ positive\ and\ test\ positive}{Number\ who\ are\ disease\ positive}$$

This is also called the true positive rate.

Similarly, the number of patients who do not have the disease and test negative plus the number of patients who test positive, but do not have the disease (the sum of column Disease Absent) gives us the specificity which is mathematically expressed as:

$$Specificity = \frac{Number\ who\ are\ disease\ negative\ and\ test\ negative}{Number\ who\ are\ disease\ negative}$$

The manner in which these tables can be used to calculate sensitivity and specificity are illustrated in the following group of tables.

(a)

	Disease		
Test 1	Positive	Negative	Total
positive	4	5	9
negative	1	90	91
Total	5	95	100

(b)

	Disease		
Test 2	Positive	Negative	Total
positive	0	0	0
negative	5	95	100
Total	5	95	100

(c)

	Disease		
Test 3	Positive	Negative	Total
positive	2	0	2
negative	3	95	98
Total	5	95	100

	Sensitivity	Specificity
Test 1	0.8	0.95
Test 2	0.0	1.0
Test 3	0.4	1.0

These tables allow us to calculate the relative sensitivity and specificity of each of the tests illustrated in the tables above. The test shown in (a) will detect 4/5 of the patients who have the disease and give a negative test results in 90/95 of those who do not have the disease. This gives us a sensitivity of 0.8 and a specificity of 0.95. In table (b) the test is basically useless as no patients with the disease tested positive, but all patients without the disease tested negative, giving a sensitivity of zero and a specificity of 1.0 (100%). The test shown in table (c) is better than that in (b) in that the sensitivity has

improved to 0.4 and the sensitivity remains 100%, but many patients subjected to this test who have the disease will not be detected. This is important since the selection of a test depends on what we want out of it. Consider that you want to detect a disease such as malignant hyperthermia where the consequences of labelling a patient negative who actually has the disease is potentially catastrophic, whereas the consequences of labelling a patient positive who is actually disease negative is relatively unimportant. The test for MH must be very sensitive, for specificity is less important. By contrast, testing for HIV needs to be both sensitive and specific.

Disease Prevalence

The prevalence of disease in a given community significantly alters the probabilities of finding the correct test result. In situations where a condition is rare, false positives are likely to exceed true positives and screening becomes pointless. Where the condition is common true positives are likely to exceed false positives and screening becomes a valid option.

This interplay between pre-test probability (the likelihood that a subject has the disease) and the sensitivity and specificity of the test influences the post test probability of getting the correct result. This interplay has been addressed in Bayes theorem which, in its simplest form, can be expressed as:

"What you thought before + New information = what you think now"

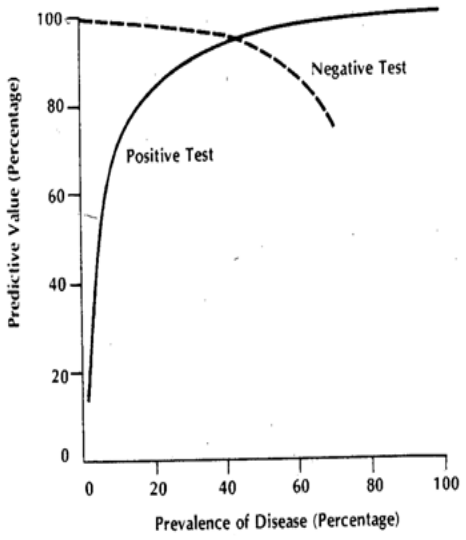
The positive predictive value of a test expresses the likelihood that test will correctly diagnose the presence of disease and is dependent on the ratio of true positives to false positives and the prevalence of the condition. It can be expressed as the probability that a subject who tests positive actually has the disease and is mathematically presented as follows:

$$PPV = \frac{P_{prev}\, X\, P_{sens}}{P_{prev}P_{sens} + (1 - P_{prev})(1 - P_{spec})}$$

Similarly, the negative predictive value expresses the likelihood that a subject who tests negative actually does not have the disease, and is of great value in assessing the reliability of a screening test in ruling out subjects likely to be disease positive.

$$NPV = \frac{(1 - P_{prev})X\, P_{spec}}{(1 - P_{prev})P_{spec} + P_{prev}(1 - P_{sens})}$$

Figure 1



Relationship between disease prevalence and predictive value in a test with 95% sensitivity and 85% specificity.
(From Mausner JS, Kramer S: Mausner and Bahn Epidemiology: An Introductory Text. Philadelphia, WB Saunders, 1985, p. 221.)

Predictive values of tests vary continuously with the prevalence of the disease and this relationship has been expressed graphically (figure 1). This diagram indicates how a test with high sensitivity and reasonable specificity performs in relationship to the prevalence of disease. Where prevalence is very low, even a very sensitive test is unlikely to yield a high proportion of positive results if applied to the whole population and the likelihood of a true positive result increases as the disease prevalence rises.

Likelihood ratios

The likelihood ratio compares the probability of a positive test in a person with a disease to the risks of finding a positive test in a person who is normal. In other words, it is the ratio of true positives to false positives. In the probability mathematical notation, it can be expressed as follows:

$$LR+= \frac{\Pr(T+|D+)}{\Pr(T+|D-)}$$

In this equation, the factor |D+ means "given the fact that the disease is present", with the "|" representing the term "given". Similarly, a negative likelihood ratio is the probability of a negative result in a patient in whom the disease is absent.

$$LR-= \frac{\Pr(T-|D+)}{\Pr(T-|D-)}$$

The likelihood ratio is a powerful tool for discriminating between sick and healthy patients. It is not dependent on pre-test probabilities but does not shed light on post test probabilities either.

Combining disease prevalence and likelihood ratio gives a very strong indication of the validity of any positive test. This can be readily done by the nomogram proposed by Fagan (Figure 2). In this nomogram a line drawn from the disease prevalence column through the likelihood ratio centre column will give an indication of the probability that the patient actually has the disease. Thus, in a patient with a 50% risk of having a condition, a test with a likelihood ratio of 20 will give a diagnostic prediction in excess of 95%.

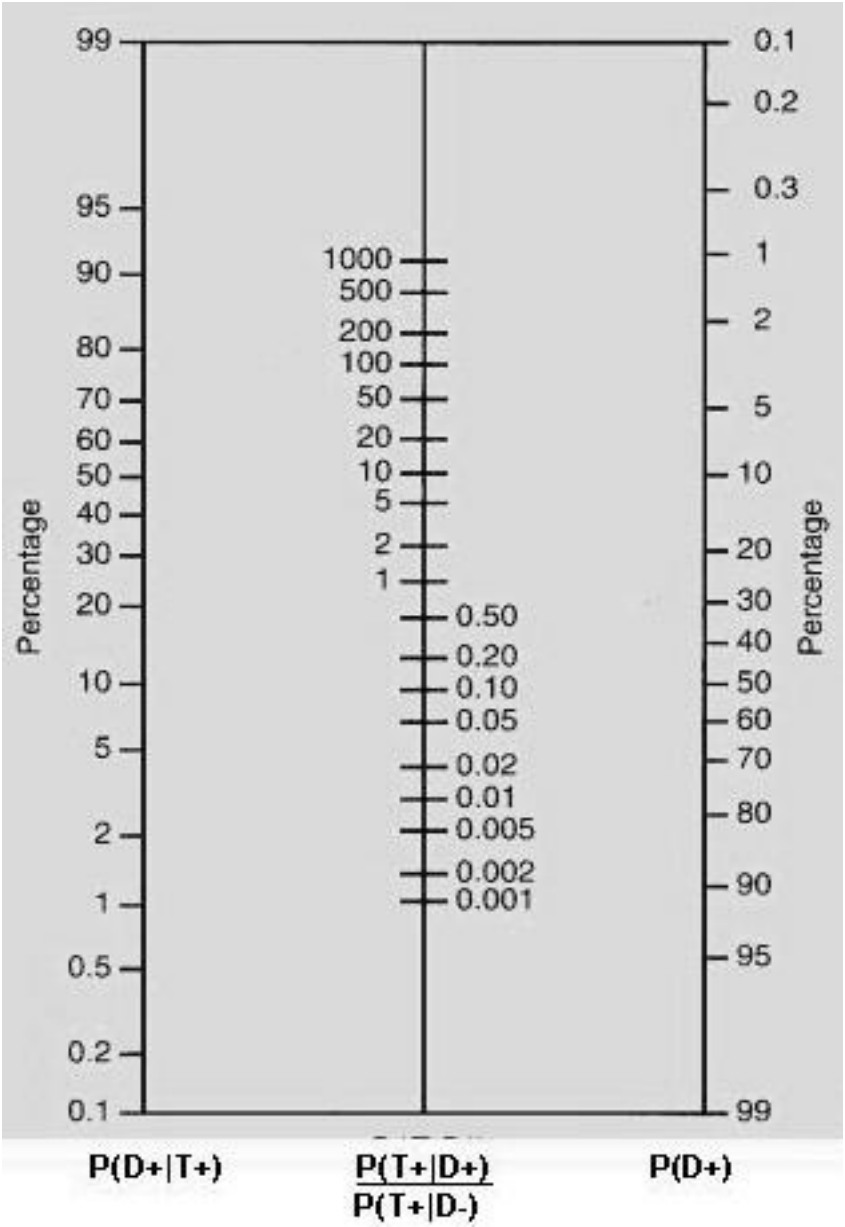


Figure 2. The Fagan nomogram for estimating the influence of disease prevalence and likelihood ratio on the probability of obtaining a correct test result.

Cut-off Points

The ideal would be to have a test where there is a clear cut off point between the healthy population and those with a disease. Unfortunately, real life is seldom like that and there is generally a considerable overlap between the healthy and diseased populations that is difficult to interpret. The normal compromise is to set an arbitrary figure for a cut off that is an acceptable trade-off. A test with a high sensitivity is "sensitive to disease" and has a low false negative rate. A test with a high specificity is "specific to health" and has a low false positive rate. However, there is a constant trade off between sensitivity and specificity (figure 3).

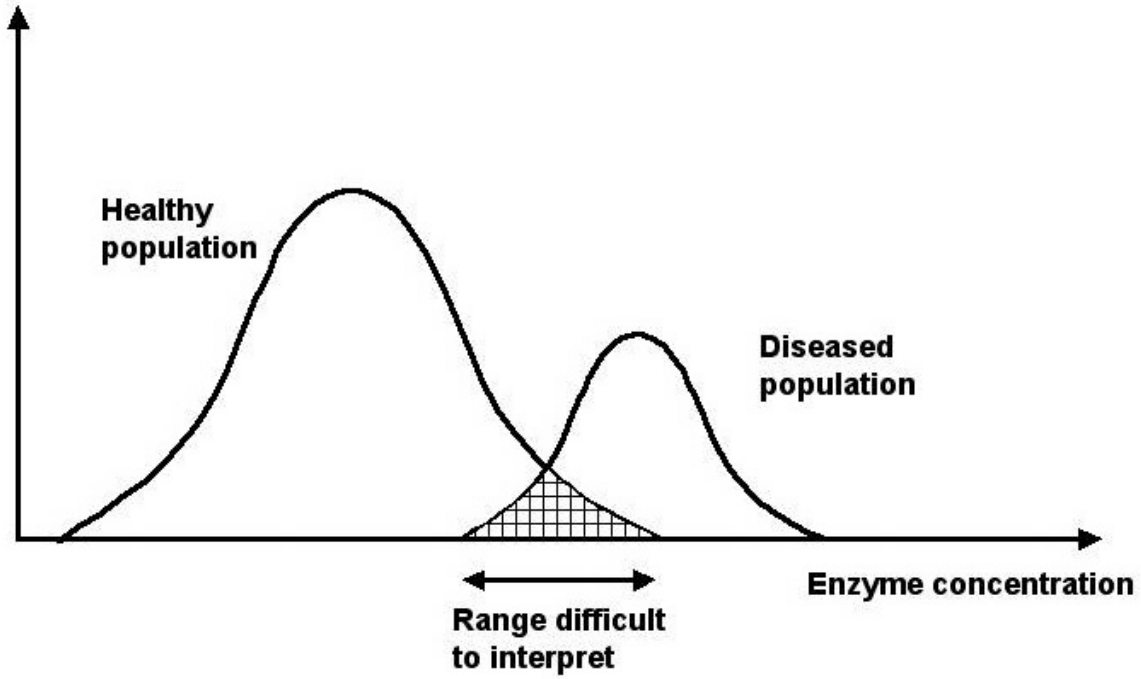


Figure 3. A real-life distribution showing that healthy and diseased populations overlap for any given test.

Shifting the cut off point to the left to obtain greater sensitivity by decreasing the false negative rate will inevitably increase the false positive rate and decrease specificity. Similarly, shifting the cut off point to the right will decrease the number of false positives and improve specificity, but will result in a greater number of false negative results and reduced sensitivity.

Receiver Operating Characteristic Curves

This kind of plot of the true positive rate against the false positive rate was introduced during the Second World War after the bombing of Pearl Harbour in an attempt to quantify the risks of radar operators either missing incoming aircraft (false negatives) or wrongly detecting aircraft that were not there (false positives). The area under the curve (AUC) can be used to quantify the overall value of any given test in terms of detecting true positives and false positives.

In an ROC plot, sensitivity (or true positive rate) is plotted along the ordinate and the false positive rate (1 - specificity) on the abscissa. The 45° line from 0 to 100 percent is the "line of identity" and represents a 50/50 ratio between true and false positives – in other words it is no better than flipping a coin. As the curve moves towards the upper left-hand corner, the sensitivity and specificity both improve. This test can be used to set cut off points, as the greatest distance described by the curve from the line of identity indicates the best compromise cut off point. And ROC curve can also be used for comparing different tests and demonstrating the superiority of one over the other. The advantages of ROC curves are that they provide a holistic picture of the relative accuracy of the test and are not dependent on disease prevalence. They do not provide a single cut-off point, but can be used to set the best compromise. However, they are not very intuitive and can't be used for individual patients.

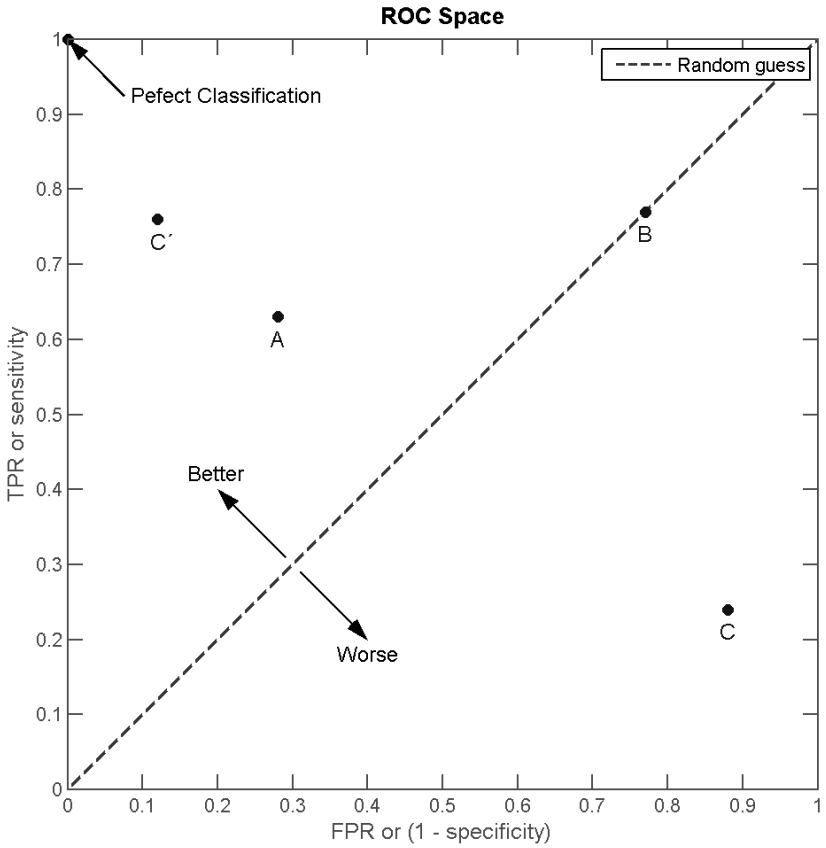


Figure 4. ROC curve. As the plot of sensitivity against 1-specificity improves, the curve moves upward and to the left.

Conclusions

All tests have limitations that are determined by the sensitivity of the test, its specificity and the prevalence of disease. In using tests to determine practice, it is important to understand the limitations of these tests and how best to use those limitations the advantage of your patient.

Further reading

1. Coetzee JF. Evaluating diagnostic tests. South African Journal of Anaesthesia and Analgesia, 10 (5): 7-15, 2004.

Peripheral Nerve Stimulators
Physical principles and clinical applications

Dr Aneet Kessow

Private Practice
Honorary lecturer- University of Cape Town

Peripheral Nerve Stimulators (PNS) are used to:

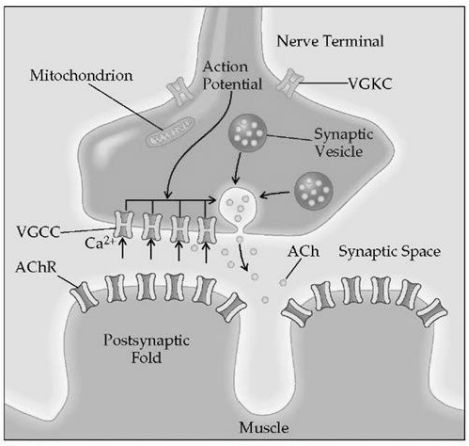
Monitor neuromuscular blockade

- During induction of anaesthesia for intubation
- During surgery to guide repeated doses of muscle relaxants to assess the depth of relaxation
- To differentiate between different types of block
- At the end of surgery to assess the ability of reversal
- At the end of anaesthesia or in recovery to assess the degree of residual blockade

Peripheral nerve identification

- To help identify peripheral nerves for nerve mapping
- To help identify peripheral nerves for nerve blockade
- To help prevent intraneural nerve injection of local anaesthetic

An understanding of neuromuscular junction electrophysiology is vital to understanding the clinical application of PNS.



Why is monitoring so important?
Undetected Residual neuromuscular block is common in the recovery room. Up to 42 % of patients receiving intermediate acting non-depolarising muscle relaxants arrive in with a TOF ratio of less than 0.7. Standard clinical criteria do not reliably detect residual blockade and standard of care has shifted the accepted TOF ratio to 0.9 or greater. Residual neuromuscular blockade contributes to greater adverse respiratory events, greater chance of re-intubation, longer recovery stay and ICU admission.

Properties of an electrical nerve stimulator

The PNS generates a standard electrical pulse, which should be *Supramaximal* – A supramaximal stimulus is a stimulus that is greater than that needed to activate all the nerve fibres in a nerve. A stimulus of 20-25% more than that needed to generate a maximal clinical response is usually used. Electric stimulation is the most commonly used but theoretically magnetic can also be used.

Constant current not voltage generator
A current setting of 60 MA will achieve supramaximal stimulation in most cases. The level of current passing through the nerve between electrodes, not the voltage, achieves nerve stimulation. The resistance in the patients skin is influenced by:

- Electrode gel dries or makes poor contact
- The patient's level of expiration changes
- Changes in patient body temperature – resistance increases as the skin temp cools

Current delivered by constant current stimulators remains the same even when the patient 's resistance changes compared to constant voltage stimulators, thus ensuring supramaximal stimulation. Current output should be limited to less than 80 MA to prevent tissue damage.

The *Rheobase* is the minimal current required to stimulate the nerve with a long pulse.

Monophasic rectangular waveform
Monophasic and rectangular waveforms are essential to prevent multiple nerve stimulations. Assuming a square pulse of the current is used to stimulate the nerve, the total energy (charge) applied to the nerve is a product of the intensity of the current and the duration of the pulse.

Duration of stimulus
Chronaxy is the property whereby a current must flow for a minimum time before the nerve tissue will depolarise no matter how high the current may be. The chronaxy time is about 80 Usec in mammalian motor nerve.

The chronaxy can be used as a measure of the threshold for any particular nerve and it is useful when comparing different nerves or nerve fibre types. Certain nerves have a different chronaxie based on their physical properties (myelination, size, etc). Also, certain patient conditions, such as diabetes, have an effect on chronaxy.

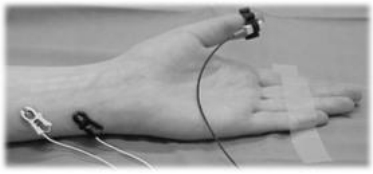
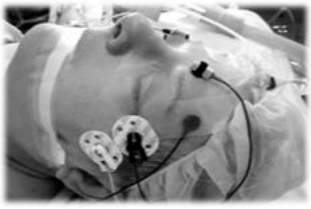
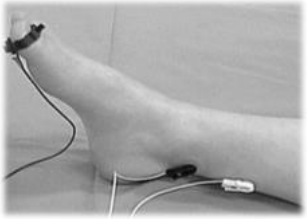
Safety and ergonomic features

- Portability
- Warning when the set current is not delivered
- Display of polarity – so that the negative electrode can be placed distally for maximal response.
- Different stimulus patterns available
- Default to lower current options when attached to needle electrodes or a stimulating needle

Placement of Electrodes:

The electrodes should be placed over the path of the peripheral nerve. The negative (black) electrode is the activating stimulating electrode, and the most effective stimulation is obtained when placed closest to the muscle terminus. The positive electrode (red) is placed 2cm proximally.

Common sites for placement appear below:

DIAGRAM	NOTES
	Nerve: Ulnar nerve Muscle: Adductor pollicis Action: Thumb adduction Black: 1-2cm proximal to wrist crease Red: 2-3cm proximal to black
	Nerve: Facial nerve Muscle: Orbicularis oculi and Corrugator supercilii Action: Twitching of eyelid and eyebrow Black: Just anterior to tragus Red: Lateral to outer canthus of eye
	Nerve: Posterior tibial nerve (sural nerve) Muscle: Flexor hallicus brevis Action: Plantar flexion of great toe Black: Over posterior aspect of medial malleolus, over posterior tibial artery Red: 2-3cm proximal to black

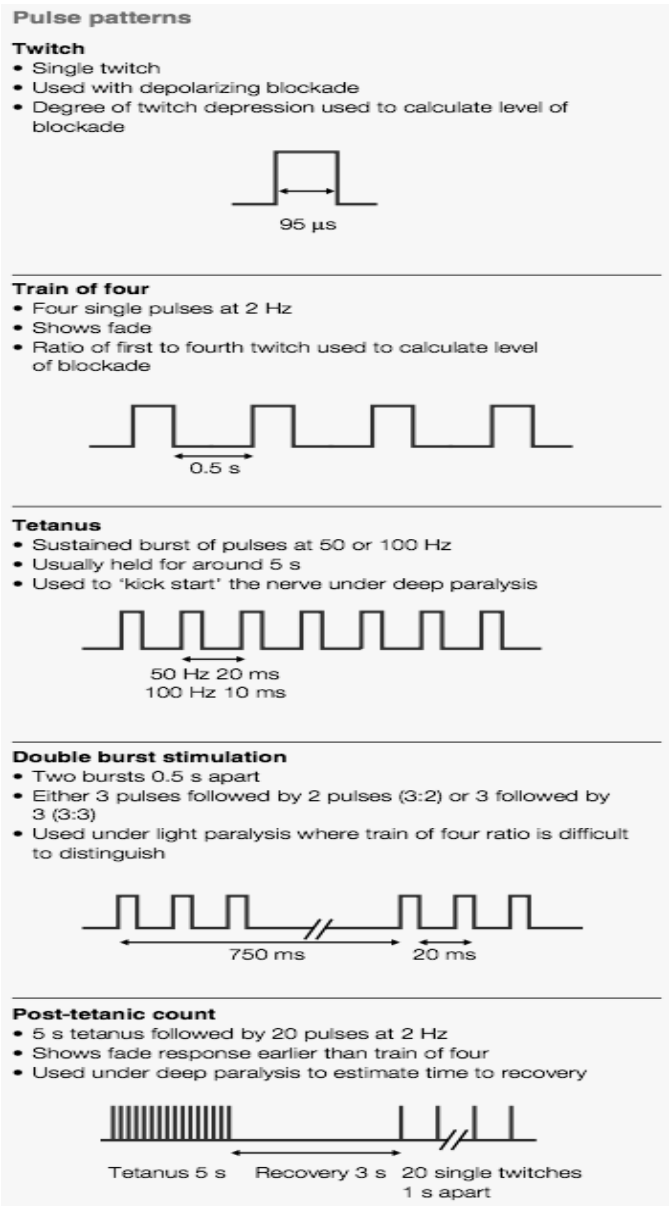
2 sites are commonly used to establish the depth of paralysis. Measurement at the adductor pollicis correlates well with the tone in the upper airway and upper oespohogeal muscles. The muscles around the eye (orbicularis oculi and corrugator supercilii) recover early (similar to the diaphragm) and a TOF of 4 here is often correlated with a TOFC of 2 or less at the adductor pollicis.

Patterns of stimulation

Single twitch
An electrical pulse is delivered at 1Hz, and the ratio of the evoked twitch compared with that before muscle relaxation gives an indication of neuromuscular blockade. When 75% of the post junctional Ach receptors are occupied by NMBA, twitch magnitude starts to decrease. When there is 100 % occupation, no twitch is elicited.

Useful for monitoring of post junctional receptor, as for deep relaxation required for intubation.

Train of four
Four pulses are given at a frequency of 2Hz or 0.5 seconds apart, potentially eliciting 4 twitches (T1-T4). The ratio of the first to the last (T1:T4) indicates the degree of neuromuscular block. Non depolarising neuromuscular blocking agents (NMBA) occupy receptors producing a decrease in magnitude of the first twitch compared with a pre relaxant stimulus and a progressive decrease in magnitude of T1 compared to T4 (Fade). At 75% occupancy T4 disappears. Similarly at 80, 90 and 100 % occupancy T3, T2 and T1 disappear. With recovery the twitches reappear in reverse order.



TOF ratio is the ratio of T1 vs. T4
TOF count is a numerical count of twitches elicited with a TOF stimulus

Clinically accepted values for TOF count:

1 twitch for intubation
1-2 twitches during anaestheisa3-4 twitches before reversal of neuromuscular blockade

Double Burst Stimulation (DBS)
This consists of 2 bursts of 3 stimuli at 50 Hz with each triple burst separated by 750 ms. These appear visually as 2 separate stimuli T1 and T2, and the ratio of these is related to the TOF ratio. It is used as it is easier for the operator to interpret reliably compared to comparing the T1:T4 ratio visually.

Tetanic stimulation
The impulse at 50 Hz of 5 ms produces detectable Fade in muscle contraction, the extent of which is related to the neuromuscular block. No fade indicates no neuromuscular block . In intense neuromuscular block, TOF stimulation may elicit no twitches. Tetanic stimulation causes post-tetanic facilitation (PTP) to mobilize presynaptic Ach. Subsequent 1 Hz twitches can now overcome the high concentration of NMBA's. The number of twitches generated (i.e. the post tetanic count) reflects the degree of neuromuscular blockade.

Depolarising NMBA's react differently to the PNS modes of stimulation. They produce equal but reduced twitches in response to single twitch and TOF stimulation (the T4:T1 ratio is 1) reduced but sustained contraction with tetanic stimulation. They do not demonstrate either tetanic fade or PTP.

How do we monitor the effect of the stimulus?

The muscle response can be assesses by visual and tactile methods – these are the easiest, but can often be unreliable and inaccurate. Objective measurement of neuromuscular monitoring is the only way of accurately assessing residual neuromuscular blockade. It is conducted via quantitative measurement of the strength of contraction of a peripheral muscle in response to peripheral nerve stimulation produced by 2 stimulating electrodes. Each measurement technique measures the force of contraction either directly or by a factor proportional to that force.

Electromyography uses electrodes to record the evoked electrical response of the muscle. Stimulating electrodes are placed over the nerve and recording electrodes over the muscle being stimulated. Stimulation of the nerve results in depolarisation of the muscle and the amplitude of the compound muscle action potential is recorded and expressed as a percentage of control or as a TOF ratio. Typically the ulnar nerve is used and the electrodes are placed over the muscle of adductor pollicis. This is easily accessible but a drawback is that small movements of the hand may affect the response, as may electro cautery.

Mechanomyography uses electrodes to measure the evoked muscle response of a muscle. A small weight is suspended from the muscle to maintain isometric contraction. The tension produced on PNS is converted into an electrical signal. This gold standard is very accurate, but is difficult to set up in practice and is used mainly in research.

Acceleromyography uses Newton's second law of motion. Force equals mass times acceleration. The transducer uses a piezoelectric crystal secured to the distal part of the digit (thumb) being measured and the PNS provides the electrical stimulus (ulnar nerve). Acceleration of the distal digit is directly proportional to the force of the contraction (mass stays the same) and therefore inversely proportional to the degree of NMB.

Kinemyography uses a piezoelectric polymer sensor in the groove between the thumb and the index finger. Movement of the muscle generates a voltage in the sensor which can be measured. This is not commonly used.

Phonomyography uses a high fidelity narrow bandwidth microphone placed along side the muscle, and measure sound intensity. This is not commonly used.

Clinical evaluation of responses after administration of depolarising NMBA's

Phase 1 Block

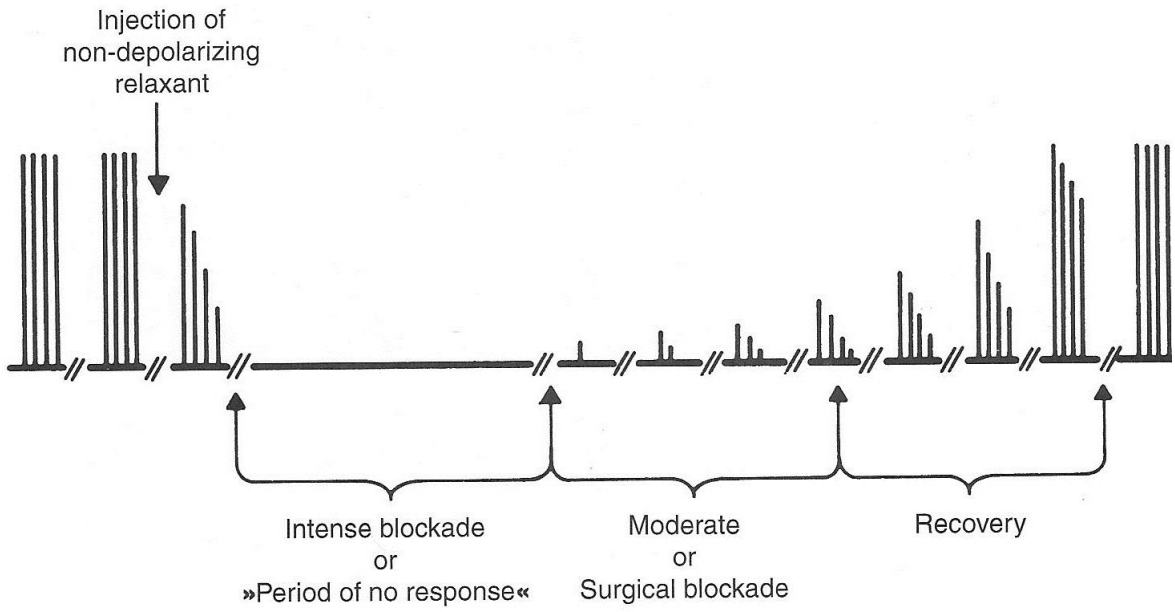
- Patients with normal plasma cholinesterase activity who receive a moderate dose of succinylcholione (0.5-1.5mg/kg).
- There is no fade during tetanic stimulation or TOF
- No PTP

Phase 2 Block

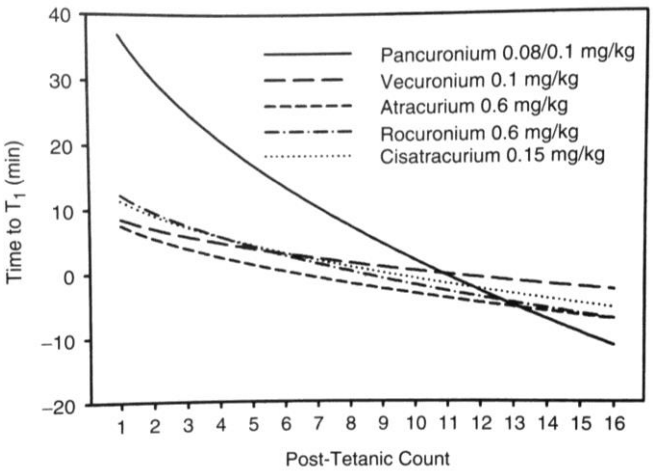
- Patients who have abnormal cholinesterase activity, who have had prolonged exposure to depolarising agents.
- Also known as mixed or dual type block, they display characteristics of non-depolarising block, i.e. fade in response to TOF or tetanic stimulation and PTP.

Clinical evaluation of responses after administering a non-depolarising NMBA

Injection of a dose of depolarising muscle relaxant to allow intubation, results in 3 levels of neuromuscular blockade (NMB), Intense blockade, moderate or surgical blockade and recovery. Different muscle groups require display degrees of relaxation during surgery and recovery, e.g. intubation requires intense NMB or abdominal wall relaxation moderate NMB for surgery.



Intense NMB
Time to intubating dose depends on the drug and dose administered.
There will be no repose to single twitch or TOF.
The duration of this period is dependant on patient and drug factors.
The PTC can be used to predict the appearance of the first twitch during this period. Clinically this may be applicable where a large dose of muscle relaxant is given and the case is subsequently cancelled.



Moderate or Surgical Blockade
This begins with the appearance of T1 and ends when T4 appears.

Recovery
The recovery phase starts once T4 appears i.e. less than 75 percent of receptor sites are occupied by NMBA.

When the TOF ratio is greater than 0.4 it becomes very difficult to assess the presence of fade without objective monitoring. The DBS may help in this situation.

Different muscle groups recover at different rates, which may have clinical implications in evaluating residual weakness after administration of NMBA.

Depth of Block	Posttetanic Count	Train-of-Four Count	Subjective Train-of-Four Ratio	Measured Train-of-Four Ratio
Intense (profound) block	0	0	0	0
Deep block	≥ 1	0	0	0
Moderate block	NA	1–3	0	0
Light (shallow) block	NA	4	Fade present	0.1–0.4
Minimal block (near recovery)	NA	4	No fade	> 0.4 but < 0.90
Full recovery (normal function)	NA	4	No fade	≥ 0.90–1.0

NA = not applicable

What TOF ratio indicates recovery from NMBA?
Previously a TOF ratio of 0.7 was though to be adequate for sufficient recovery in the postoperative period.

This correlates with clinical signs as below:

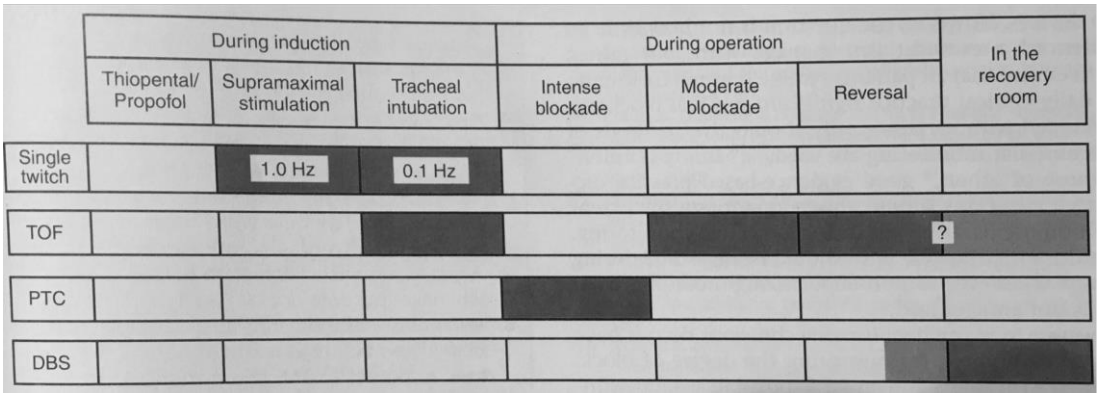
Clinical tests of postoperative muscular recovery

Unreliable
Sustained eye opening
Protrusion of the tongue
Arm lift to opposite shoulder
Normal tidal volume
Normal or near normal vital capacity
Maximum inspiratory pressure <40-50 cm H_2O
Reliable
Sustained head-lift for 5 seconds
Sustained leg lift for 5 seconds
Sustained hand grip for 5 seconds
Sustained "tongue depressor test"
Maximum inspiratory pressure ≥40-50 cm H_2O
(Normal swallowing?)

- TOF ratios below 0.7 are a significant risk factor for postoperative pulmonary complications.
- TOF ratios of between 0.7-0.9 decrease chemoreceptor sensitivity to hypoxia
- TOF ratios of less than 0.9 are associated with increased risk of regurgitation and aspiration, diplopia, and subjective feelings of weakness.

Residual neuromuscular blockade is inadequate neuromuscular recovery as measured by objective neuromuscular monitoring which may show a TOF ratio of less than *0.9*

What Nerve Stimulator mode to use when ?



? = TOF is less useful in the recovery area unless some form of objective monitoring is used

Applicability with Sugammadex

Sugammadex is a modified gammacyclodextrin that binds aminosteroid NMB's (rocuronium > vecuronium > pancuronium). Because of the 1:1 molar ratio between sugammadex and the aminosteroid NMBA, there has to be sufficient sugamadex molecules administered to encapsulate ALL the free molecules of the NMBA. The TOFC may be useful to determine the most appropriate dose to ensure full reversal. At a TOFC count of 1-3, a dose of 2 mg/kg will reliably produce TOF>0.9 in 2 minutes. For reversal of deep blockade (PTC >1), a dose of 4 mg/kg is recommended. For Profound block (PTC=0), a dose of 16mg /kg is recommended.

Key points:

- Clinical evaluation of recovery of neuromuscular function has limitations.
- Residual neuromuscular weakness has significant morbidity.
- Absence of fade does not exclude significant residual block.
- Objective neuromuscular monitoring is important.
- Clinically significant residual neuromuscular blockade is less likely if the TOF ratio (as measured objectively) is greater than 0.9.

Learning Questions:

Which of the following is the most reliable pattern to determine residual neuromuscular blockade?

a) TOF <0.7
b) TOF <0.9
c) Clinical signs
d) No fade present visually

A 45 year old male is anaesthetized for a 4 hour long elective Neurosurgical procedure. After induction with 1mg/kg of rocuronium, it is discovered that the patient has not stopped their clopidogrel as originaly planned, and the surgery is cancelled. What would be the best clinical course to follow:

a) ventilated the patient for at least 2 hours and assess for first movements
b) Use the TOF count after an hour and ventilate the patient in ICU or recovery if no change.
c) Use sugammadex at a dose of 1mg/kg
d) Use the PTC to establish when the first switch will appear, and a TOFC to establish the dose of sugammadex that will be effective.

The properties of an ideal nerve stimulator would ideally be :?

a) A Monophasic and rectangular waveforms, that is constant current, of adequate chronaxy, and which work with batteries.
b) A multi waveform, constant current, short duration machine which is built into the anaesthetic machine, with electrodes over the radial nerve.
c) A constant voltage, long duration waveform of greater than 80 mA, with electrodes over the Temporalis muscle.
d) A constant current, greater than 80 mA, providing supramaximal stimulus until contraction occurs.

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4. Monitoring Neuromuscular Transmission, Torda, Anaesthesia and Intensive care , Vol 30 , No 2 . 2002
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6. Current Status of Neuromuscular Reversal and Monitoring: Challenges and Opportunities. Brull, Anaesthesiology, January 2017. Vol.126, 173-190.
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Notes:

Local Anaesthetics

Dr Renier Verbeek

Private Practice
Honorary lecturer- University of Cape Town

Cocaine is the only naturally occurring local anaesthetic, found in the Andes, West Indies and Java and was introduced to Europe in the 1800's. In 1860, cocaine was extracted from the leaves of the Erythroxylon coca bush. Interestingly, Sigmund Freud used cocaine on some of his patients, but became addicted through self-experimenting.

Halsted was the first person to use cocaine for nerve blocks, in 1885, but also became addicted through self-experimentation.

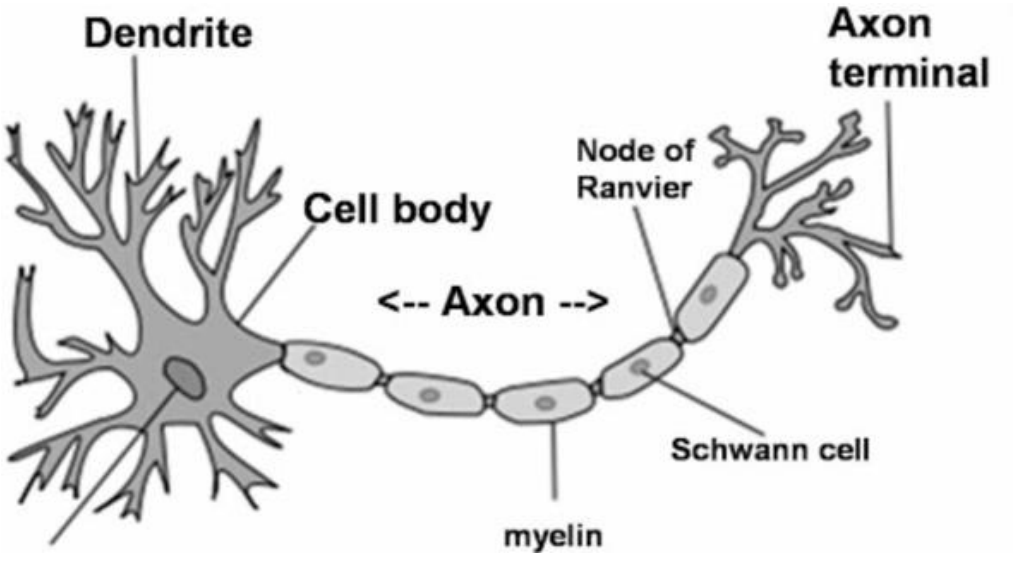
Procaine was the first synthetic local anaesthetic in 1904. Procaine was only available as a powder and had to be dissolved before injected. It also had a short duration of action. Amethocaine was released in 1930. These agents were esters and, despite a risk of allergic reactions, were widely used.

During the 1940's one third of all surgeries (in Sweden) were performed under local and regional anaesthesia, with toxicity posing a major risk when well perfused tissues were injected. Surgeons had to be vigilant for spasms and convulsions (that were treated with barbiturates). Lignocaine was synthesized in Stockholm by Nils Löfgren in 1943, he gave the compound to his self-experimenting assistant, Bengt Lundqvist, to try. It was used during the latter stages of the Second World War. Lignocaine is an amide and had a low risk of allergic reactions. This was followed by mepivacaine (1957), prilocaine (1960), bupivacaine (1963), ropivacaine(1997) and levobupivacaine (2000).

Physiology

Neurones have a resting potential value of approximately -70 mV. The resting potential is determined by the concentrations of the ions on both sides of the cell membrane and the ion transport proteins. Sodium influx is necessary for the depolarization of nerve cell membranes and propagation of impulses.

The axons of neurones are wrapped by myelin and separated in segments, these intervals are known as nodes of Ranvier. It is produced by Schwann cells exclusively in the peripheral nervous system, and by oligodendrocytes exclusively in the central nervous system. The myelin sheath reduces membrane capacitance and increases membrane resistance in the inter-node intervals, thus allowing a fast, saltatory movement of action potentials from node to node.



Formulation

Local anaesthetics are formulated as the **hydrochloride salt** to render them water soluble. Multidose vials often contain preservatives, but carry the risk of producing arachnoiditis when injected in the spine. Single-dose ampoules without additives (apart from glucose at 80 mg/ml used in 'heavy' bupivacaine) are suitable for subarachnoid administration.

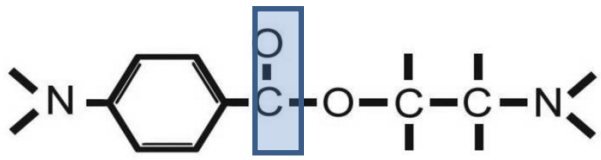
Most local anaesthetics are **racemic** mixtures except levobupivacaine and ropivacaine, where the s-enantiomer is used, which is less toxic, more potent and longer acting. **Liposoma**l Bupivacaine (Exparel) is a longer acting form of Bupivacaine, where the bupivacaine is delivered via a multivesicular liposomal system.

Mechanism

Local anaesthetic action is dependent on intracellular blockade of the voltage gated Na+ channels. Unionised lipid-soluble drug passes through the phospholipid membrane where it is ionised. In its ionised form it binds to the Na+ channel, preventing it from leaving the inactive state. The degree of blockade in vitro is proportional to the frequency of depolarization, local anaesthetic bind to 'open' Na+ rather than inactivated channels.

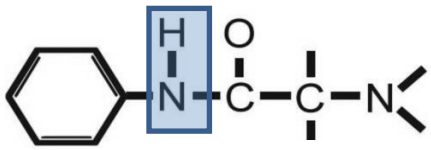
'Membrane expansion' offers an additional mechanism of action. Unionised drug dissolves into the phospholipid membrane and may cause swelling of the Na+ channel/lipoprotein matrix, resulting in its inactivation.

Local anaesthetics are weak bases and exist predominantly in the ionised form at physiological pH, as their pKa exceeds 7.4. They fall into one of two chemical groupings, amino esters or amino amides, which describes the linkage between the aromatic lipophilic group and the hydrophilic group



Ester = Hydroxyl group (-OH) replaced by an alkyl (-O) group)

Esters



Amide = Hydroxyl group (-OH) replaced by an amine group or ammonia

Amides

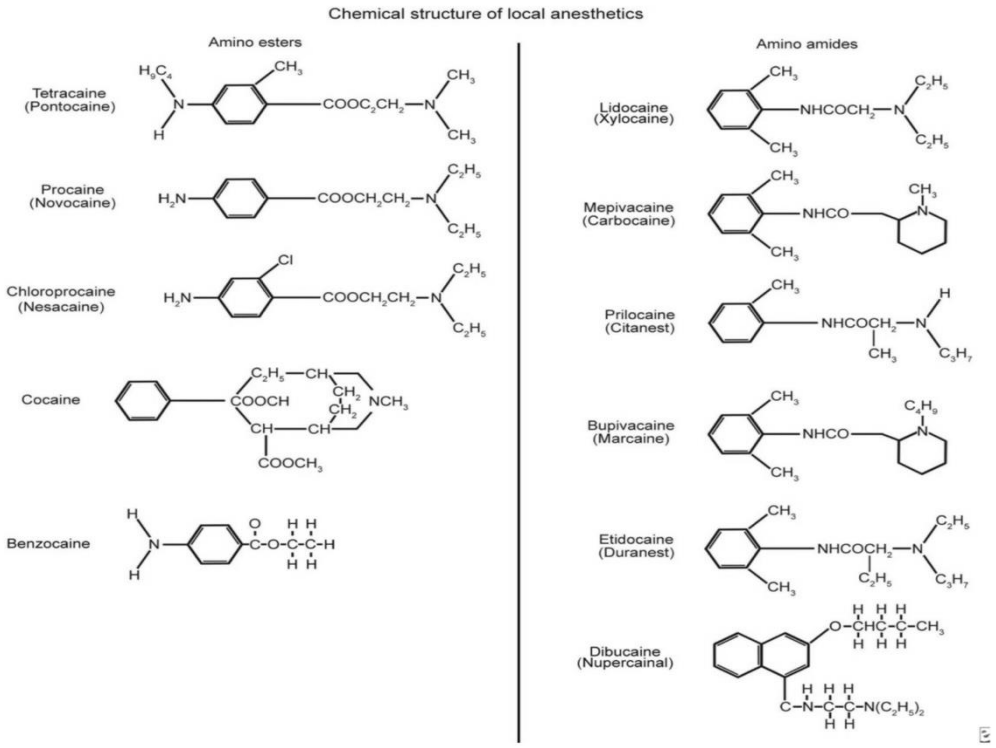
All local anaesthetic agents are ***weak bases***, they exist in two forms: ionised (BH+) and unionised (B). The pKa of local anaesthetics determines the pH at which both forms exist in equal amounts. As the pH of tissues differs from the pKa of specific drugs, more of the drug exists in either the ionised or unionised form. This is expressed in the Henderson-Hasselbalch equation:

$pKa - pH = \log [BH+] / [B]$

where [B] is the concentration of unionised and [BH+] the concentration of ionised drug.

Lignocaine has a pKa of 7.9, a high fraction is present in the unionised form and, therefore, has a fast onset of action.

Bupivacaine, with a higher pKa of 8.1, has a greater fraction present in the ionised form, which is unable to penetrate the phospholipid membrane, resulting in a slower onset of action.



(*Any local anaesthetic containing 2 i's is an amide)

Potency

Potency is correlated to lipid solubility in vitro, but less so in vivo. Factors such as vasodilator properties and tissue perfusion, determine the amount of local anaesthetic that is available at the nerve.

The duration of action is determined by its protein binding. Local anaesthetics with limited protein binding have a short duration of action and those with more extensive protein binding have a longer duration of action.

The intrinsic vasodilator activity varies between drugs and influences potency and duration of action. Vasodilatation occurs via direct relaxation of arteriolar smooth muscle fibres. In general, local anaesthetics cause vasodilatation at low concentration (prilocaine>lignocaine>bupivacaine>ropivacaine) and vasoconstriction at higher concentrations. Cocaine has vasoconstrictor actions by inhibiting neuronal uptake of catecholamines (uptake 1) and inhibiting monoamine oxidase (MAO).

Local anaesthetics are generally ineffective when used in inflamed tissue, due to a more acidic environment. The acidic environment reduces the unionised fraction of drug available to diffuse into and block the nerve. There may also be increased local vascularity, which increases removal of drug from the site.

Pharmacokinetics

Absorption

The absorption of local anaesthetics into the systemic circulation varies depending on the site of injection. This will be influenced by the characteristics of the agent used and presence of added vasoconstrictor. If local anaesthetic is injected intravascular, very high systemic levels will result and potentially cause central nervous system or cardiovascular toxicity.

Distribution

The distribution of the drug is influenced by the degree of tissue and plasma protein binding of the drug. Ester local anaesthetics are minimally bound, while amides are more extensively bound in the

plasma. Alpha–acid glycoprotein binds local anaesthetic with high affinity, although albumin binds a greater quantity due to its relative abundance. When protein binding is decreased, the free fraction of drug is increased.

The degree of protein binding will affect the amount of placental transfer. Bupivacaine is more highly bound than lidocaine, so less crosses the placenta. If the foetus becomes acidotic, there will be an increase in the ionised fraction and local anaesthetic will accumulate in the foetus (ion trapping). Ester local anaesthetics do not cross the placenta in significant amounts due to their rapid metabolism.

Metabolism and excretion
Amides are metabolised hepatically by amidases. Amidase metabolism is much slower than plasma hydrolysis and so amides are more prone to accumulation when administered by continuous infusion. Reduced hepatic blood flow or hepatic dysfunction can decrease amide metabolism.

Esters (except cocaine) are metabolized by pseudocholinesterases to inactive compounds and have a short half-life. Para-aminobenzoate is one of the main metabolites and has been associated with hypersensitivity reactions. Cocaine is hydrolysed in the liver. Ester metabolite excretion is renal.

Local anaesthetic toxicity

Local anaesthetics may be toxic if sufficient amounts are absorbed into the systemic circulation. Bupivacaine appears to be the most dangerous, although all can be harmful. The incidence of Local Anaesthetic Systemic Toxicity (LAST) has decreased significantly in the last 30 years due to increased awareness of toxicity.

Central Nervous System

Local anaesthetics penetrate the CNS rapidly and have a bi-phasic effect. Inhibitory interneurons are blocked first with initial excitatory phenomena, resulting in circumoral tingling, visual disturbance, tremors and dizziness. This is followed by convulsions. Finally, all central neurones are depressed, leading to apnoea and coma.

Cardiac

Local anaesthetic drugs block cardiac Na+ channels and decrease the maximum rate of increase of phase 0 of the cardiac action potential. They also have direct myocardial depressant properties. Lignocaine is used as an antiarrhythmic to treat ventricular arrhythmias. Bupivacaine has a prolonged binding to Na channels and therefore may lead to re-entrant arrhythmias and ventricular fibrillation. In addition, tachycardia may enhance frequency-dependent blockade by bupivacaine, which adds to its cardiac toxicity. Ca++ and K+ channels are also affected.

(*CNS toxic signs and symptoms occur at a lower serum levels than cardiac toxic levels and give a degree of advance warning as to possible cardiac toxicity).

Autonomic

When used in spinals and epidurals, local anaesthetics may block sympathetic outflow to a varying degree. This can result in hypotension requiring vasopressor support. If the cardio-accelerator fibres, that emerge from T1-T4, are blocked, bradycardia may ensue.

Cocaine is a potent vasoconstrictor and may cause problems in patients already on vasoconstricting drugs such as monoamine oxidase inhibitors.

Prilocaine is metabolised to O-toluidine, which can cause methaemoglobinaemia in susceptible individuals.

PABA ALLERGY, (a metabolite of many esters)

Unexpected local anaesthetic toxicity can occur, where the pharmacokinetics of the drug are altered due to co-morbidity such as cardiac or hepatic failure (reducing the metabolism of the drug), alterations in plasma protein binding or interactions with other drugs. .

Bupivacaine can also disrupt metabotropic and ionotropic signal transduction. They can also inhibit each of the four components of oxidative phosphorylation - i.e. substrate transport, electron transport, proton motive force maintenance and ATP synthesis

Local toxicity:

- Intraneural injection
- Neural ischaemia due to local pressure
- High dose lidocaine radicular irritation

Systemic toxicity:

- Dose injected
- Weight of patient
- Concentration of drug
- Rate of administration
- Site of injection
- Addition of a vasoconstrictor
- Degree of protein binding

Allergy

Additive toxicity

- Vasopressors
- preservatives

Pharmacology of local anaesthetic drugs

The block duration is influenced by several factors:

- Type of the drug (lignocaine – short acting; bupivacaine – long acting)
- Drug concentration (the higher the concentration, the longer the block)
- Drug volume (the larger the volume, the faster the onset and the more dense the block)
- Additives (adrenaline prolongs short acting drug action and sodium bicarbonate enhance speed of onset)
- Anatomic area (Lower limb blocks last longer than upper limb blocks. This is a function of nerve size and vascularity)

Local anaesthetics can be used topically (conjunctiva, skin, mucous membranes and ear drum). They act within minutes and last up to an hour. Toxic blood levels may occur if large areas are anaesthetized, with specific caution in small children.

When the skin is infiltrated, the action is almost immediate, owing to the small unmyelinated nerve fibres being rapidly penetrated by the local anaesthetic. Skin infiltration of plain lignocaine lasts 2 hours and plain bupivacaine lasts 4 hours. These times can be extended by adding a vasoconstrictor.

Larger nerves (e.g. sciatic) are thicker and well myelinated. The local anaesthetic takes longer to penetrate these nerves and hence the onset time is longer.

Lignocaine (lidocaine, xylocaine)

It is an amide-type local anaesthetic and was developed in 1943. This agent has been used in clinical practice for almost 70 years. It has a rapid onset of action but a relatively short duration of action. It has class 1b anti-arrhythmic properties

Kinetics

It is 70% protein bound to alpha-1-acid glycoprotein. Lignocaine has a more rapid onset of action and longer duration of action than ester-type local anaesthetics such as procaine. It is approximately 90% metabolised in the liver by N-dealkylation (cytochrome CYP1A2 and CYP3A4) to the pharmacologically active metabolites monoethylglycinexylidide and glycinexylidide.

The elimination half-life of lignocaine is approximately 1.5–2 hours in most patients. This may be prolonged in patients with ***hepatic impairment or congestive heart failure.***

Clinical usage

- Skin infiltration - 0.2–1.0 % lignocaine. Use with epinephrine 1:200,000 or 1:400,000
- Topical anaesthesia – 2% gel (Cathejell) or 4% spray (oro-pharyngeal)
- Biers block (IVRA) - 40 ml of 0.5% lignocaine (without adrenaline)
- Peripheral nerve blocks - 1–2% lignocaine (with or without adrenaline)
- Subarachnoid block – 2% lignocaine plain (no adrenaline). 5% lignocaine has been associated with transient radicular irritation (TRI) or TNS (Transient neurologic symptoms) The risk of TRI is low with the less concentrated solution
- IV administration of lignocaine suppresses the cough reflex during laryngoscopy, endotracheal intubation, extubation and bronchoscopy

The recommended maximum safe doses of lignocaine are as follows:

Lignocaine without adrenaline	**3 mg/kg**
Lignocaine with adrenaline	**7 mg/kg**

These maximum dosages are not universally accepted. Rates of absorption vary in tissues, depending on the blood flow. Body weight gives no indication of lean tissue mass. Lignocaine can be carbonated by adding sodium bicarbonate. This shortens the onset and prolongs both the intensity and duration of block.

Tumescent lignocaine anaesthesia

Tumescent lignocaine anaesthesia involves the subcutaneous injection of large volumes (up to 4 litres) of dilute lignocaine (< 1g/l) and adrenaline (< 1mg/l) and is used in surgical procedures that include breast, cutaneous, subcutaneous and vascular tissues. This is widely used in liposuctioning.

The maximum safe dose determined by the FDA is 55mg/kg (in combination with liposuctioning). A recent study measured serum lignocaine concentrations over a 24 hour period and found that the maximum safe dose for tumescent anaesthesia without liposuctioining is 28mg/kg and with liposuctioning 45mg/kg. (3)

Prilocaine (Citanest)

Prilocaine closely related to lignocaine and is very similar in its clinical action. It is rapidly metabolised and hence less toxic. It can cause methaemoglobinaemia when used in high dosage (> 600 mg). Methaemoglobinaemia causes a blue skin discolouration and results in false pulse oximeter readings. The condition is usually benign and resolves within a couple of hours. The treatment is methylene blue 1 mg/kg i.v. over 5 minutes. The clinical usage and doses are similar to those of lidocaine. Prilocaine 0.5% is the drug of choice in Biers block.

The recommended maximum safe doses of prilocaine are as follows:

Prilocaine without adrenaline 6 mg/kg
Prilocaine with adrenaline 9 mg/kg

Bupivacaine (Marcain)

Kinetics

Bupivacaine has a pKa of 8.1, with a slow onset of action. Bupivacaine is the most protein-bound (95%) amide local anaesthetic, which is the reason for its long duration of action. It is metabolised in the liver by N-dealkylation to pipecolylxylidine and pipecolic acid.
It is remarkably stable in solution and is commercially available in 0,1%, 0.25% , 0.5% solutions (with and without adrenaline) and Spinal heavy bupivacaine (0.5% bupivacaine + 6% glucose)(80 mg/ml glucose (specific gravity 1.026)). Bupivacaine is four times more potent than lignocaine. Therefore, 0.25% bupivacaine is equipotent with 1%lignocaine. Bupivacaine binds tightly to tissues and thus has a long duration of action (up to 24 hours in some cases). Adding adrenaline will ***decrease its toxicity*** by delaying the drug absorption but will have ***minimal effect on the duration*** of the block.

The recommended maximum safe doses of bupivacaine are as follows:

Bupivacaine without adrenaline **2.0 mg/kg**
Bupivacaine with adrenaline **2.5 mg/kg**

Levobupivacaine (Chirocaine)

Bupivacaine is a racemic mixture of the R and S enantiomers. Levobupivacaine contains the S enantiomer only. Compared with bubivacaine it has greater vasoconstrictive action and less motor block. It is less cardiotoxic.

The pKa of 8.1 for levobupivacaine is the same as that of bupivacaine. Protein binding is more than 97%, mainly to alpha-1-acid glycoprotein.

It is extensively metabolised, with no unchanged levobupivacaine detected in the urine or faeces. Cytochromes CYP3A4 and CYP1A2 metabolise levobupivacaine to desbutyl levobupivacaine and 3-hydroxy levobupivacaine, respectively. The 3-hydroxy levobupivacaine appears to undergo further transformation to glucuronide and sulphate conjugates.

(not licensed for subarachnoid injection)

The recommended maximum safe dose of levobupivacaine is:

Levobupivacaine **2.5–3.0 mg/kg** (insufficient data)

Liposomal Bupivacaine (Exparel)

Consists of tiny lipid based particles (liposomes) which contain discrete water-filled chambers dispersed through a lipid matrix (DepoFoam technology). The liposomes consist of biodegradeable cholesterol, triglycerides and phospholipids. Fusion and division of the multivesicular liposomes allow the internalized drug to be released in a delayed fashion. This results in extended release of bupivacaine and has up to 72 hours duration of action.

The initial approval by the FDA was for bunionectomies and haemorrhoidectomies, followed by later approval for local wound infiltration and TAP blocks, in 2015.

The maximum safe dose of Liposomal Bupivacaine is 266mg.

Ropivacaine (Naropin)

Ropivacaine is an amide local anaesthetic produced in three concentrations (2, 7.5 and 10 mg/ml). It is a 99% pure S-(-) isomer, produced by “membrane separation synthesis”

Ropivacaine is highly plasma protein binding (94%) and the lipid solubility lies somewhere between that of lignocaine and bupivacaine. The duration of action and onset time are similar to those of bupivacaine. The analgesic potency of ropivacaine is 0.60 (0.47-0.75) relative to bupivacaine. Claims for reduced motor block must be considered with differences in analgesic potency in mind.
Studies have demonstrated that ropivacaine is less neuro- and cardiotoxic than bupivacaine.
Ropivacaine is extensively metabolised by the cytochrome P450 system in the liver to 3 and 4-hydroxy-ropivacaine, both of which have some local anaesthetic activity.

Concerns about bupivacaine’s toxicity led to the development of ropivacaine. It has been used clinically for the past decade. Clinical evidence indicates that it is less cardiotoxic than bupivacaine..

The addition of adrenaline or sodium bicarbonate does not appear to alter the speed of onset or duration of the block. The intensity and duration of the motor block are lower than with bupivacaine. It is slightly less potent than bupivacaine (in peripheral nerve blockade, 0.5% bupivacaine is equipotent with 0.6% ropivacaine). It is not currently licensed for subarachnoid usage.
The recommended maximum safe dose of ropivacaine is:

Ropivacaine without adrenaline	**3mg/kg**
Ropivacaine with adrenaline	**4mg/kg**

Local anaesthesia additives

Adrenaline, clonidine and sodium bicarbonate can be added to local anaesthetic agents. They prolong the duration and intensity of the block, as well as reducing the risk of local anaesthetic toxicity.

Adrenaline

Adrenaline causes vasoconstriction, which reduces the local anaesthetic absorption and results in prolonging the block duration and reducing toxicity. Adrenaline ***does not significantly prolong the duration of bupivacaine or ropivacaine*** but it does slow the absorption of these agents and thus reduces peak plasma levels. This reduces the toxicity risk of these two local anaesthetics.

Adrenaline is available in two ampoule sizes:

- A 1 ml ampoule containing 1 mg (i.e. 1:1000)
- A 10 ml ampoule containing 1 mg (i.e. 1:10,000)

(Adrenaline 1:200,000 solution contains 5 micrograms per ml)

Use with caution in cases of serious ischaemic heart disease, thyrotoxicosis and hypertension. In such cases, it would be prudent to avoid adrenaline all together. Remember that adrenaline reduces the peak local anaesthetic blood levels but this varies with the site of block. For instance, absorption occurs rapidly following an intercostal block but more slowly from a brachial plexus block. Adrenaline-containing local anaesthetic solutions give an early warning of accidental intravascular injection.

Clonidine

Clonidine is an alpha-2 adrenoreceptor agonist. It prolongs and intensifies blocks when added to local anaesthetics. Adding clonidine 75–100 micrograms can extend the duration of peripheral blocks by 50–100%. For Biers blocks (IVRA), clonidine 150 micrograms can be added to the local anaesthetic solution. It reduces tourniquet pain and causes no adverse effects when the tourniquet is released. Clonidine is regularly used when prolonged postoperative analgesia is required.

Sodium bicarbonate

Sodium bicarbonate is added to local anaesthetics to raise the pH of the solution. This has the effect of increasing the proportion of unionised local anaesthetic, enabling it to penetrate the nerve membranes more readily. Thus, the speed of onset is increased. It also prolongs the duration and intensity of the block. Bicarbonate reduces the pain of injection (injection pain is associated with a low pH and cold solution). The recommended dose is 1 ml of 8.4% sodium bicarbonate per 10 ml of local anaesthetic. There is little advantage in adding it to bupivacaine or ropivacaine. Overzealous alkalinisation may result in precipitation of the local anaesthetic molecules.

DRUG	LIGNOCAINE	PRILOCAINE	BUPIVACAINE	LEVOBUPIVACAINE	ROPIVACAINE
Description	Amide	Amide	Amide	Amide	Amide
Relative potency	2	2	8	8	6
Onset	5-10 min	5-10 min	10-15 min	10-15 min	10-15 mins
Duration without Adrenaline	1-2 hours	1-2 hours	3-12 hours	3-12 hours	3-12 hours
Duration with Adrenaline	2-4 hours	2-4 hours	4-12 hours	4-12 hours	4-12 hours
Max dose without Adrenaline	3 mg/kg	6 mg/kg	2 mg/kg	2.5 mg/kg *	3 mg / kg *
Max dose with Adrenaline	7 mg/kg	9 mg/kg	2.5 mg/kg	3 mg/kg *	4 mg / kg *

* INDICATES PROBABLE SAFE MAXIMUM DOSE (INSUFFICIENT DATA).

Local Anaesthetic Toxicity

Dose Limits ($mg.kg^{-1}$)

Agent	Plain	+ Adrenaline
LIDocaine	3	7
BUPivacaine	2	2.5
PRILocaine	6	9
ROPivacaine	3	4

NB:
- Toxic dose limits assume normal plasma protein binding, hepatic & renal function, and no drug interactions
- Max. safe dose of Adrenaline = 4 $\mu g.kg^{-1}$
- 1% solution of any drug = 1 $g.100\,ml^{-1}$ = 10 $g.l^{-1}$ = 10 $mg.ml^{-1}$ (so 0.5% BUPivacaine contains 5 $mg.ml^{-1}$)
- 1:1000 solution of any drug = 1 $mg.ml^{-1}$ (so 1:200 000 Adrenaline = 5 $\mu g.ml^{-1}$)

Symptoms

Tinnitus
Circumoral tingling
Metallic taste in mouth

Dizzyness, Dysphoria, Dysarthria
Sudden alteration in mental status
Severe agitation or loss of consciousness

Cardiovascular collapse
Bradyarrhythmias or tachyarrhythmias

NB:
Toxicity may occur some time after initial injection

Management

Immediate actions:
Stop administering local anaesthetic
Call for help
Maintain airway, intubate if necessary
Give 100% oxygen
Hyperventilation may be beneficial
Confirm/establish iv access
Control seizures:
- small incremental doses of benzodiazepine, thiopental or propofol

Reassess ABC

If not in cardiac arrest:
Treat hypotension and arrhythmias as appropriate
(Do not use lidocaine as an antiarrhythmic agent)
Consider intravenous lipid emulsion

If in cardiac arrest:
Commence CPR
Treat hypotension and arrhythmias as appropriate
(Do not use lidocaine as an antiarrhythmic agent)
Arrhythmias may be very refractory to treatment
Consider cardiopulmonary bypass if available

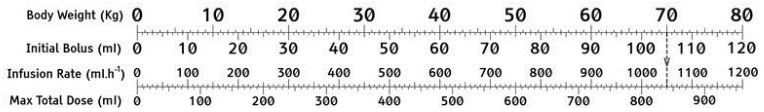
Give intravenous lipid emulsion (20%):
Initial bolus of 1.5 $ml.kg^{-1}$
AND commence infusion at 15 $ml.kg.h^{-1}$
(see nomogram below)

After 5 minutes:
If cardiovascular stability has not been restored, or circulation deteriorates:
Repeat the bolus
AND increase the rate of infusion to 30 $ml.kg.h^{-1}$

After another 5 minutes:
If cardiovascular stability has not been restored, or circulation deteriorates:
Repeat the bolus for a third, final time

Continue the infusion until patient's condition improves
Do not exceed a maximum cumulative dose of 12 $ml.kg^{-1}$

Nomogram for Intravenous lipid (20%) administration for Local Anaesthetic Toxicity



(6)

Intralipid 20%

TREATMENT FOR LOCAL ANESTHETIC-INDUCED CARDIAC ARREST

In the event of local anaesthetic-induced cardiac arrest, unresponsive to standard therapy, Intralipid 20% should be given IV in the following dose regime:

- **– Intralipid 20% 1.5mL/kg over 1minute**
- **– Follow immediately with an infusion at a rate of 0.25mL/kg/min,**
- **– Continue chest compressions,**
- **– Repeat bolus every 3-5 minutes up to 3 mL/kg total dose until circulation is restored**
- **– Continue infusion until hemodynamic stability is restored. Increase the rate to 0.5 mL/kg/min if BP declines**
- **– A maximum total dose of 8mL/kg is recommended**

<u>An adult weighing 70kg</u>:

- ***– Take a 500ml bag of Intralipid20% and a 50ml syringe.***
- ***– Draw up 50ml and give stat i.v. and repeat x 1***
- ***– Then attach the Intralipid bag to an iv administration set and run it IV over the next 15 minutes***
- ***– Repeat the initial bolus up to two times – if spontaneous circulation has not returned.***

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Intermediary Metabolism

Dr Howard Radford

Private practice
Lecturer- Dept of Anaesthesia
University of the Witwatersrand

Disclaimer

These notes have not been peer reviewed. Please refer to appropriate text books and journal articles.

The basic building block of the human body is the cell. Normal cell function requires turgor, energy to maintain pumps, systems to protect against extremes of pH and free radicals, processes to manufacture basic building blocks of structures and enzymes and removal waste products.

Metabolism refers to all chemical and energy transformations that occur. The chemical reactions within the cells is called **intermediate metabolism**. The chemical reactions of metabolism are organized into pathways, in which one chemical is transformed through a series of steps into another chemical. This process is driven by enzymes. Catabolism breaks down substrates and liberates energy. Anabolism is a process that takes up energy and builds up cellular components such as protein, nucleic acids, lipids and some carbohydrates.

Energy

Energy liberated by catabolism is not utilised directly by the cells but is used in the formation of ester bonds between phosphoric residues and certain organic compounds e.g. adenosine guanosine cytidine and uracil. Adenosine triphosphate [ATP] is the most common energy store Its breakdown [ATP → ADP → cAMP] liberates energy. Other compounds include guanosine triphosphate [GTP] cytidine triphosphate[CTP] uridine triphosphate[UTP] and inosine triphosphate [ITP] Creatine Phosphate and Acyl CoA compounds.

Most ATP is produced by oxidative phosphorylation that occur in the mitochondria. Oxidative phosphorylation involves the transfer of hydrogen from NADH to the flavoprotein FAD generating ATP from ADP and further along the flavoprotein cytochrome system a further 2 ATP are generated. Oxygen acts as the final acceptor of the electron and is thus an important regulator of oxidative phosphorylation. See figure 1

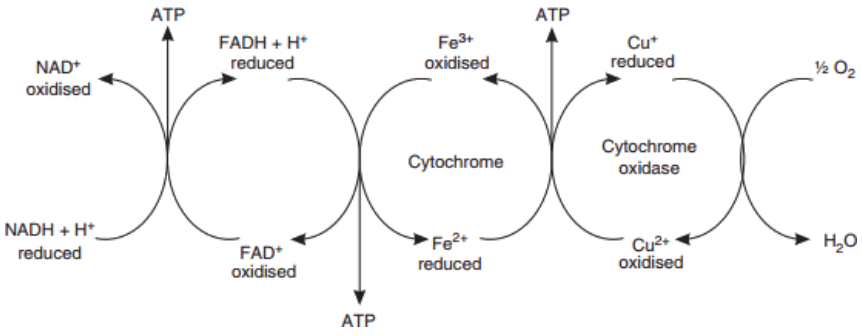


Fig. 1. Electron transport chain – oxidative phosphorylation

Glucose metabolism

Glucose catabolism

Glucose to Glucose 6 phosphate.
Glucose enters the cell via Glut receptors. In the cytosol it is converted Glucose 6 phosphate [G6P]. [Glucose → G-6-P]. One ATP is required. In the liver this is mediated by the enzyme glucokinase which has high specificity for glucose and its activity is enhanced by insulin. In other cells in the body Glucose → G-6-P is mediated by hexokinase. This process may be reversed in the liver and to a lesser extent in the kidney by the enzyme glucose 6 phosphatase. This process cannot be reversed in all other cells.

Fate of Glucose 6 phosphate.
G6P may be converted to glycogen, shunted to the hexose monophosphate pathway [Pentose phosphate pathway] or enter the glycolytic in pathway.

a. Glycogen.
The conversion to the storage form of glycogen occurs predominantly in the liver and skeletal muscle. This is mediated by insulin.

b. Hexose monophosphate pathway.
G6P entry into the pathway is facilitated by the enzyme glucose 6 phosphate dehydrogenase [G6PD] This pathway produces NADPH + H. The NADPH is required for biosynthetic reactions such as fatty acid synthesis, cholesterol synthesis, drug reduction, and as a cofactor for some non-synthetic enzymatic reactions. [Used in Glutathione reductase protects against free radicles] In addition, it is used for the production of ribose for nucleotide and nucleic acid synthesis. The hexose monophosphate shunt also allows the entry of some carbohydrates into the glycolytic pathway (especially ribose). Steroidogenic tissues, red blood cells, and the liver are the major sites of hexose monophosphate pathway. The process occurs in the cell cytoplasm.

c. ***Glycolytic Pathway***.
This pathway is illustrated in the figure 2. This process takes place in the cytoplasm. Some important aspects are highlighted in the text that follows.

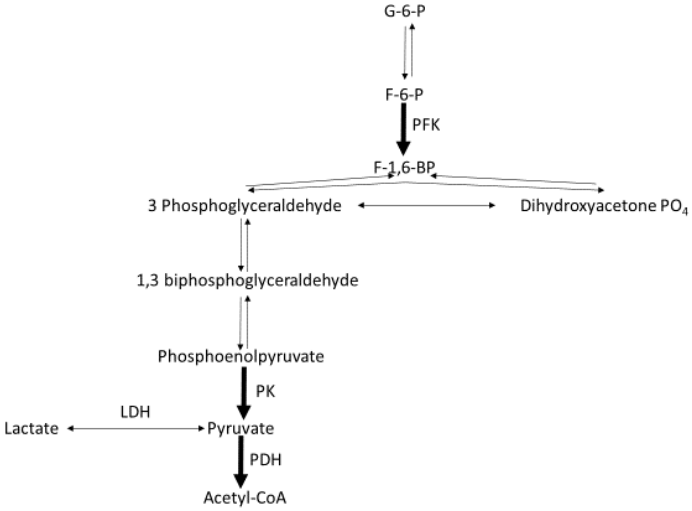


Fig. 2. Glycolytic pathway

Glucose 6 phosphate → Fructose 1,6 Biphosphate [F-1,6-BP]

G6P→ Fructose 6 phosphate [F-6-P] which is then converted to F-1,6-BP. This requires one ATP. This reaction is mediated by phosphofructose kinase [PFK]. Glucose will be completely degraded to pyruvate after this reaction has taken place. It is thus known as the committed step. When ATP or energy is plentiful in the cell, PFK is inhibited and the breakdown of glucose for energy slows down. Therefore, PFK can regulate the degradation of glucose to match the energy needs of the cell. It is also inhibited by citrate and FFA.

This process needs an alternative enzyme to reverse it Fructose- 1,6 - biphosphatase

Fate of Fructose 1,6 biphosphate.
F-1,6-BP under the influence of aldolase, the fructose molecule is spilt into 2 isomers each with 3 carbons

→ dihydroxy acetone [DHAP]
→ 3phosphoglyceraldehyde

These molecules are interconvertible the net result is 2 molecules of 3-phosphoglyceraldehyde are produced. In the next step another ATP is consumed and a NADH is generated in the production of 1,3 biphosphoglyceraldehyde. 1,3 biphosphoglyceraldehyde continues along the pathway to the formation of pyruvate, generating 2 ATP. In the erythrocyte some 1,3 biphosphoglyceraldehyde may be converted to 2,3 biphosphoglyceraldehyde which is important in oxygen transport.

Fate of pyruvate
Pyruvate is transported into mitochondria by a pyruvate transporter. It is a simport, where the hydrogen ion is transporter. In the mitochondria two different enzymes are involved based on the presence or absence of oxygen.

Pyruvate dehydrogenase [PDH].
Lactate dehydrogenase [LDH].

In the absence of oxygen, Pyruvate is converted to lactate and NAD^+ by lactate dehydrogenase - anaerobic metabolism.

In the presence of oxygen pyruvate is converted to Acetyl-CoA by pyruvate dehydrogenase. PDH is a multienzyme complex. PDH is located in the matrix space of mitochondria. The Enzyme contains 3 enzymatic sub-units and 5 co-enzymes.
Co-enzymes of PDH complex include:

Thiamine PyrPhosphate (TPP)
Lipoic acid
Flavin Adenine Dinucleotide (FAD)
CoEnzyme~A
Nicotinamide Adenine Dinucleotide (NAD^+)

During the reaction 2 NADH and 2 FADH are produced and enter the electron transport chain producing ATP. A deficiency of thiamine will result in enzyme dysfuction and pyruvate will be converted to lactate. Elevated levels of ATP, NADH and FADH will inhibit the enzyme.
This process cannot be reversed and needs a bypass step i.e. oxaloactetate malate shuttle

d. Citric acid cycle

The Citric acid cycle takes place in Mitochondrial Matrix. Acetyl-CoA condenses with oxaloacetate [OAA] to give rise to citrate. Eight enzymes of the citric acid cycle catalyse a series of well-known organic reactions that cumulatively oxidize citrate to oxaloacetate, two CO2 molecules, with the concomitant generation of three NADH one FADH2 and one GTP. see figure 3

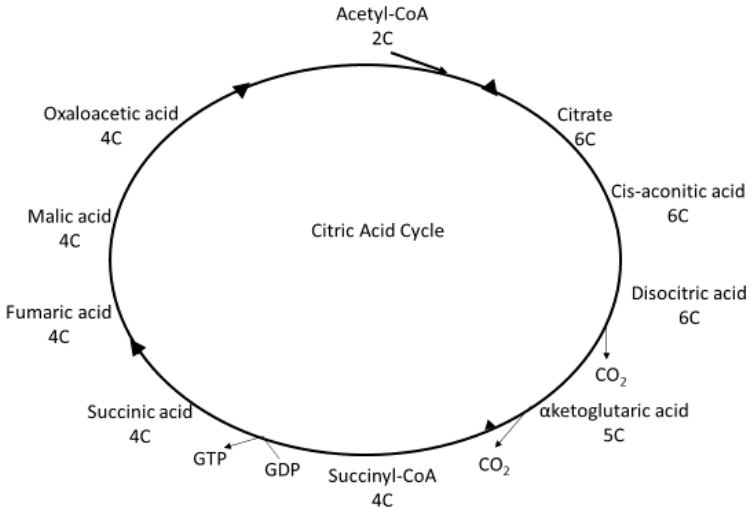


Fig. 3.

Besides its role in aerobic metabolism of glucose the citric acid cycle receives inputs from fatty acid breakdown which produces Acetyl CoA. Many amino acids after transamination enter the cycle at various points. Glutamic acid enters at the level of α-ketoglutarate, and aspartate enters at oxaloacetic acid level. Those amino acids which are converted as members of citric acid cycle can enter the gluconeogenesis pathway through oxaloacetate.

38 ATP are produced by glucose metabolism. The glycolytic pathway glucose to pyruvate produces 2 ATP, the conversion of pyruvate to Acetyl- CoA 6 ATP and 24 ATP are produced by the electron transport chain because of formation of FADH and NADH by the citric acid cycle. A further 6 ATP are generated from NADH formed in the glycolytic pathway

Most texts suggest that no ATP is formed directly by the citric acid cycle. The only energy rich compound formed directly by the citric acid cycle is GTP.

Glucose anabolism

The human body maintains glucose levels either by dietary intake, breakdown of glycogen - glycogenolysis or by gluconeogenesis. Gluconeogenisis occurs mostly in the liver and to a lesser extent in the renal cortex and small intestines. It is a metabolic path which results in the production of glucose from non-carbohydrate carbon substrates such as amino acids, lipids and from other steps in metabolism including lactate and pyruvate. [lactate, glycerol, alanine and glutamine accounts for 90% of precursors] Synthesis of glucose from pyruvate utilizes many of the same enzymes as glycolysis. Three reactions of Glycolysis have forward direction that are essentially irreversible. These steps must be bypassed in Gluconeogenesis. Two of the bypass reactions involve simple hydrolysis reactions.

a. Glucokinase or Hexokinase is reversed by Glucose-6-phosphatase so that G6P is converted to glucose.
b. Phosphofructokinase is reversed by Fructose-1,6-bisphosphatase so that F-1,6-BP is converted to F-6-P.

Pyruvate Kinase is reversed by 2 enzymes acting in concert
Pyruvate Carboxylase [requires biotin as a coenzyme]
PEP Carboxykinase

This process requires a large amount of energy.

Pyruvate dehydrogenase is bypassed using the malate / oxaloacetate shuttle. Oxaloacetate in the mitochondria may be converted back to malate which diffuses out of the mitochondria into the cytoplasm and then converts back to oxaloacetate which is then converted to Phosphoenolpyruvate

Lactate is formed mainly in the muscle and the erythrocyte. It is carried to the liver where lactate is converted to pyruvate and then glucose which is then returned to the body via the blood stream - the Cori cycle.

Transamination or deamination of Amino acids facilitate the entry of the carbon skeleton into the glycolytic pathway and citric acid cycle at several points.

Hydroxyproline, serine, cysteine, threonine, glycine → pyruvate
Tryptophan → alanine→ pyruvate
Tyrosine, phenylalanine, aspartate →fumarate
Isoleucine, methionine, valine →succinyl CoA
Histidine, proline, glutamine and arginine all convert to glutamate → αketoglutarate

Alanine and glutamine constitute 60% of all amino acids released by the muscle. This amount is out of proportion of their relative abundance in muscle. They are not only released by muscle but also synthesized from other amino acids (threonine, serine, hydroxyproline, cysteine and glycine give rise to alanine, whilst histidine, proline and arginine give rise to glutamine)

Triglycerides [TG]
TG are made up of fatty acids and glycerol. When TG are catabolised, they are broken down into Free fatty acids and glycerol.

Glycerol enters the glycolytic pathway via dihyrdoxyacetone phosphate.

Free fatty acids are made of unbranched carbon or branched carbon chains. If the Carbon chain of the fatty acid molecule is branched the branch is degraded by α oxidation to give rise to unbranched chains. Unbranched chains are degraded by βoxidation i.e. 2 carbons are cleaved off at a time and produces NADH. If the chain consists of an even number of carbons the end product is 2 Acetyl-CoA. If the Carbon chain consists of an odd number of carbons the product of βoxidation will result in Acetyl-CoA and Acetoacetyl-CoA which is converted to acetoacetate and then acetone and β hydoxybuyrate [ketone bodies]. Acetyl-CoA formed enters the citrate cycle and produces energy via the electron transport chain. This process takes place in the mitochondria.

Fat metabolism

Biologically important lipids are triglycerides phospholipids [cell membrane] and sterols [steroid hormones and cholesterol]. TG are made of 3 fatty acids bound to glycerol Naturally occurring contain an even number of carbon atoms They may have saturated [no double bonds] or be unsaturated [have double bonds]. 3 polyunsaturated fats are essential for normal development. These are Linoleic, Linolenic and Arachidonic acid. They are precursors of prostaglandins

Fatty acid catabolism

The degradation of fatty acid chain is described briefly above

Fatty acid anabolism

Fatty acids are synthesised in the cytosol. Acetyl-CoA is transported from the mitochondria into the cytosol. Cytosolic Acetyl-CoA is converted into Malonyl-CoA by acetyl-coA and a carboxylase. Biotin and NADPH are important co factors This is the committed step in the process. Once Malonyl-CoA is formed under the influence of an enzyme Fatty acid synthase two carbon chains are added at a time to the malonyl until a 16-carbon chain Palmityl is formed which then leaves the cycle. Triglycerides are formed when one glycerol molecule combines with 3 free fatty acids.

Urea cycle

Deamination of amino acids results in the formation of NH_3 [ammonia]

In the liver NH_3 +HCO_3 +ATP give rise to carbomoyl phosphate which enters the mitochondria and combines with ornithine to give rise to citrulline. Citrulline is converted to arginine which is converted back to ornithine and urea is liberated. In liver disease urea formation decreases and NH_3 increases.

References

Available on request

Suggested Article

Any basic physiology text book some good websites are available.

Notes:

Defence of the Intravascular Volume

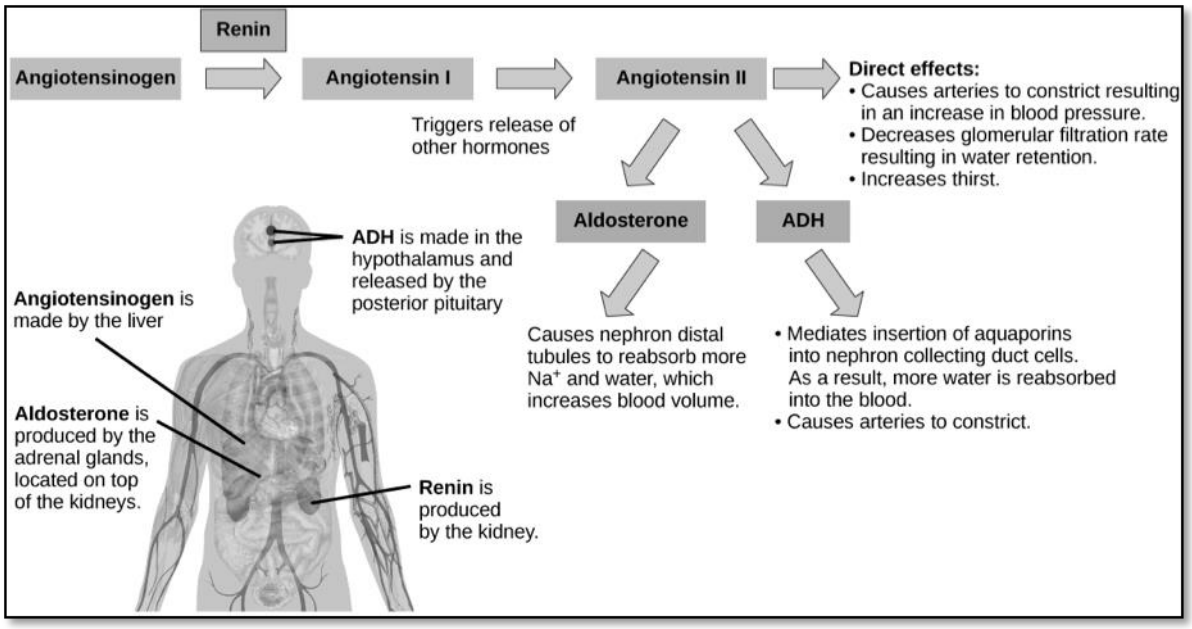
Dr Estie Cloete

Dept of Anaesthesia & Perioperative Medicine
University of Cape Town

This lecture will discuss the importance of the RAAS and Natriuretic systems in the homeostatic control of arterial blood pressure, tissue perfusion, and extracellular volume, as well as its influence in the thirst response and the compensatory mechanisms in haemorrhagic shock.

The natriuretic peptide system forms part of the regulation of extracellular fluid composition and volume. It not only impacts on the salt and water handling but also influence blood pressure regulation. Natriuretic peptides (NP) also has an influence on the myocardial structure and function. The main physiological action is a reduction in blood volume and systemic vascular resistance that lead to reduction in arterial pressure.

To understand the importance of the natriuretic peptides, we need to revise the RAAS (Renin-Angiotensin-Aldosterone-System).



The extracellular fluid volume is determined by the osmotically active solute in the extracellular fluid (ECF). Sodium and Chloride is the most abundant solutes and the changes in Chloride is usually secondary to changes in sodium. The most important determinant of the ECF volume is sodium. The control of water excretion is controlled by volume and a rise in the volume will inhibit Vasopressin secretion and vice versa. The osmotic regulation of Vasopressin secretion is overridden by volume stimuli.

Angiotensin II (ATII) has got an important role in the response to hypovolemia. Angiotensin II will stimulate Vasopressin and Aldosterone secretion. It causes blood vessel constriction and thirst that will help to maintain the blood pressure. With the expansion of the ECF volume, the natriuretic peptides ANP and BNP gets secreted. This will lead to natriuresis and diuresis.

Two natriuretic peptides secreted by the heart: ANP and BNP.

ANP is primarily released from atrial myocardial cells and in some cases the ventricles in response to atrial stretch from volume expansion. ATII, endothelin and sympathetic stimulation especially ß adrenergic mediated, carotid and baroreceptors also stimulates ANP release. Both atria participate in the release of ANP, but it appears that the right is more important in quantity. ANP can be isolated from other tissues like the brain where ANP- containing neural pathway projects from the anteromedial part of the hypothalamus to the lower brainstem which controls neural regulations of the

cardiovascular system. ANP opposes ATII and the ANP-containing neural circuits is involved in lowering the BP and promoting natriuresis.

Brain natriuretic peptide is homologous to ANP and initially identified in the brain but also present in the cardiac ventricles. This 32-amino acid molecule is present in circulation in concentrations 20% lower than that of ANP in normal subjects but exceed ANP in diseased states. The prohormone proBNP gets cleaved and then produces the active hormones BNP and N-terminal proBNP(NT-proBNP).

C-type natriuretic peptide is a paracrine mediator and is produced by vascular endothelial cells and present in the pituitary and kidneys with very little in the circulation and heart. The function may involve regulation in blood flow, but its physiological role remains to be determined.

Mechanism of action

The two major actions of NP are

- Vasodilatory effects
- Natriuresis and Diuresis via the renal system

1. Vasodilator effects

ANP and BNP causes systemic vasodilation via cGMP on vascular smooth muscle. Venodilation with the increased venous compliance will lead to a decrease the central venous pressure and preload and thus a reduction in the cardiac output. Arterial dilatation leads to decrease in systemic vascular resistance (SVR) and arterial blood pressure

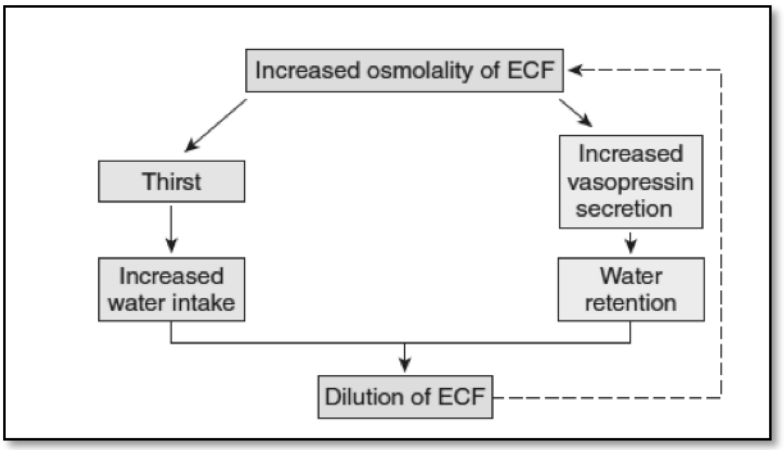
2. Renal effects

ANP and BNP increase sodium excretion by the kidney through dilatation of the afferent arterioles and relaxation of the mesangial cells. This then leads to an increase in glomerular filtration and inhibition of sodium reabsorption in the renal tubules. In the RAAS these peptides inhibit renin secretion and counteract the pressor effects of the catecholamines and ATII.

In summary: Natriuretic peptides is a counter-regulatory system for the RAAS.

REGULATION OF ECF TONICITY

Maintenance of the extracellular fluid (ECF) tonicity is a function of 1. thirst and 2. Vasopressin (ADH) mechanisms. When the osmotic pressure of the plasma rises, ADH is secreted and thirst is stimulated. This leads to water retention and increased water intake to maintain tonicity.



Thirst

The physiological urge to drink water is influenced by social, habitual, psychogenic and cultural factors. Thirst, which provides motivation to drink, is an important component of the coordinated sequence of physiological responses that maintain the volume and composition of body fluids.

The 4 major stimuli to thirst are:

- Hypertonicity
- Hypovolemia
- Hypotension
- Angiotensin II

With regards to hypertonicity, the cellular dehydration acts via osmoreceptor mechanism in the hypothalamus, while the low-pressure baroreceptors in the right atrium and great vessels senses hypovolemia. High pressure baroreceptors in carotid sinus and aorta senses hypotension and angiotensin II is stimulated via renin and the response to renal hypotension.

When water is lost from the body, it usually depletes the extracellular as well as the intracellular compartments. Compensatory responses will attempt to minimize the changes in body fluid volume and composition change. These include:

- ADH secretion
- RAAS stimulation
- Sympathetic activation
- Reduced renal solute and water excretion

ADH (Vasopressin)

Vasopressin receptors, V_{1A}, V_{1B} and V_2 are G-protein coupled. Vasopressin causes retention of water by increasing the collecting ducts permeability. Water enters the hypertonic interstitium of the renal pyramids and urine becomes concentrated, but its volume decreases i.e. retention of water in excess of solute so osmotic pressure is decreased.

V2 receptors is responsible for the antidiuretic effect, together with aquaporin 2 inserted into the membranes of the collecting ducts

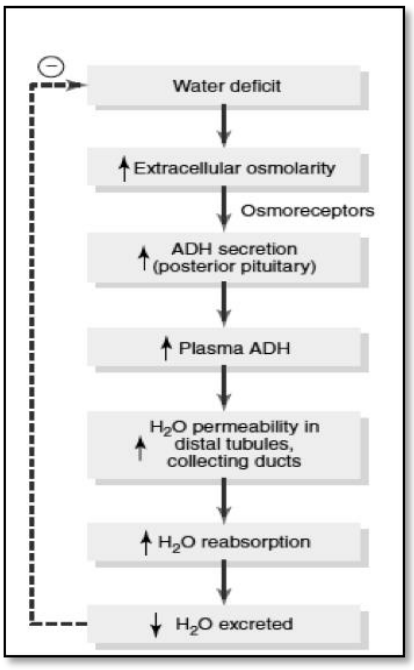
V_{1A} receptors are found on the vascular smooth muscle through which it exerts the vasoconstrictor effect and also acts in the brain and spinal cord, as a neurotransmitter. In the liver it causes glycogenolysis.

V_{1B} receptors increase secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary.

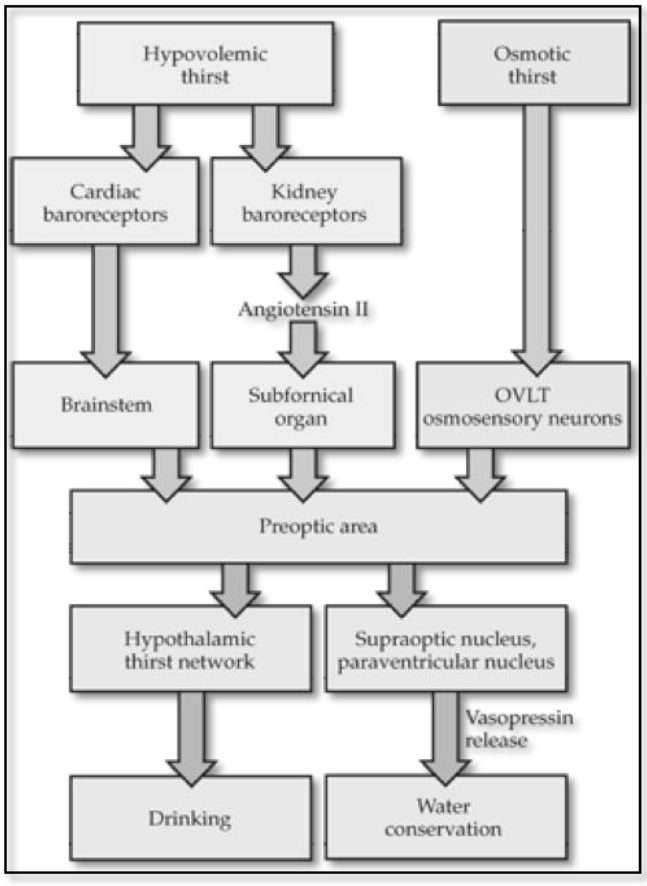
Increased Vasopressin Secretion	**Decreased Vasopressin Secretion**
↑ Plasma Osmotic pressure	↓ Plasma Osmotic pressure
↓ ECF volume	↑ ECF volume
Exercise, Sympathetic stimulation	
Standing	
Angiotensin II	
Carbamazepine	Alcohol

The feedback system

Control of extracellular sodium concentration via Osmoreceptors. As the extracellular osmolarity increases(↑[Na]), osmoreceptors in the anterior hypothalamus shrink. A nerve signal is send to the posterior pituitary where the action potential causes a release of ADH. Via the bloodstream to the kidneys, it increases water reabsorption. The opposite is true when the extracellular fluid is hypoosmotic.



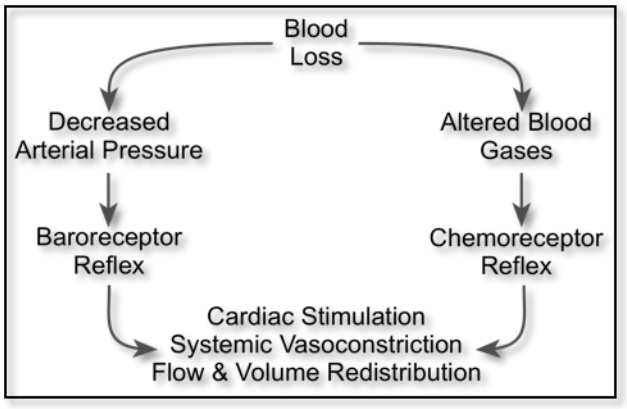
In summary: Hypovolemic and osmotic thirst lead to drinking and water conservation via ADH release.



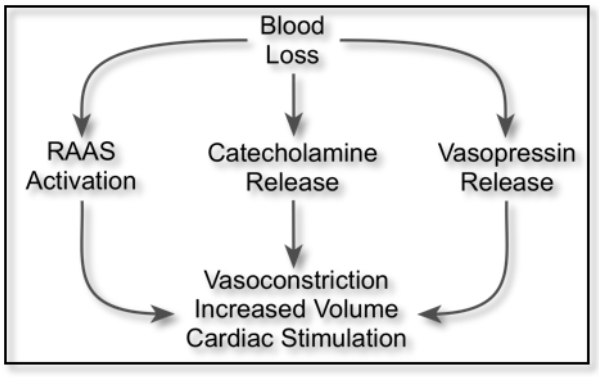
Hemorrhagic shock

The cardiac output is responsible to meet the metabolic demands of the tissues. With progressive loss of circulating volume, there is a redistribution of flow to the brain and myocardium. Decrease in venous return and atrial pressure activates baroreceptors in the carotid sinus and aortic arch. Decreased input inhibits parasympathetic activity and enhances the sympathetic system. This leads to an increase in cardiac output due to change of SVR to maintain tissue perfusion. There are a number of compensatory mechanisms activated to restore arterial pressure and perfusion of tissues:

- Baroreceptor reflexes
- Chemoreceptor reflexes
- Circulating vasoconstrictors
- Renal reabsorption of sodium and water
- Activation of thirst mechanisms
- Reabsorption of tissue fluids



Baroreceptors are activated by a decrease in arterial pressure. This leads to sympathetic activation to cause vasoconstriction (Increase SVR) and inotropy of the heart. The cardiac output is redistributed to the brain and myocardium. Systemic acidosis triggers the chemoreceptor reflex with reinforce the actions of the baroreceptors on the heart and vascular system.



Humoral mechanisms are activated by arterial hypotension and sympathetic activation. The stimulation of the adrenal glands, leads to the release of catecholamines and renin is released from the kidneys. This leads to ATII and Aldosterone release and lead to vasoconstriction, increased sympathetic activity, ADH release, activation of thirst response, and increased renal reabsorption of sodium and water. With hypotension there is a decrease in capillary hydrostatic pressure and less fluid leaves the capillaries.

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Functional Anatomy of the Kidney

Dr Kotie Bester

Dept of Anaesthesia & Perioperative Medicine
University of Cape Town

Endocrine functions

- 1,25 dihydroxycholecalciferol
- Erythropoietin
- Renin
- Kinins
- Prostaglandins

The kidney has a glomerular filtration rate (GFR) of 100-150 ml/min (i.e. 150-180 l per day). 65% of reabsorption and secretion happens in the proximal convoluted tubule (PCT). 80% of reabsorption is completed by the point where the collecting duct starts.

Blood flow to the kidney = 20-25% of CO.
High cortical blood flow with low O_2 extraction ratio – filtration.
Low medullary blood flow (to maintain concentration gradient) with high O_2 extraction ratio (to supply metabolic processes) – at risk of ischaemic injury.

NEPHRON

A unit = nephron
= glomerulus + tubule
There are about 1.3 million nephrons per kidney.

Glomerulus

A **glomerulus** consists of a tuft of capillary, supplied by an afferent arteriole, and drained by an efferent arteriole. It is folded into the **Bowman's capsule** (a dead tubular end), and together they form the **corpuscle**.

Three layers form the barrier between the endovascular lumen and the "tubular" lumen:
Endothelium – basal membrane (BM) – epithelium
Mesangial cells, where present, are on the endothelial side:
Endothelium – mesangial cells – BM – epithelium

Mesangial cells:
- Stellate cells
- "Pericytes" are cells in the walls of capillaries all over the body – mesangial cells are pericytes.
- Functions:
  - Contraction – can decrease the filtration surface through distortion of capillaries (see table 1)
  - Secretion – renin
  - Take up immune complexes, therefore can cause disease

Endothelial cells:
- Fenestrated, with pores 70-90nm in size.
- 50 times more permeable than capillaries in skeletal muscle.

Epithelial cells:
- Podocytes wrapped around capillaries.
- Filtration slits of about 25nm, covered with a thin membrane, are formed between the pseudopodia.

Neutral substances of 4nm will pass freely, and above 8nm will not pass. Negatively charged molecules are repelled by the negatively charged sialoproteins in the capillary wall. All three layers (endothelium, BM and epithelium) have enough space to allow small proteins to pass, but all three layers are negatively charged, and repel other negative charges.

Albumin (7nm, anion): only 0.2% is filtered. During nephritis, negative charges on the glomerular wall is lost, and albuminuria occurs (even without increase in "pore" size). The basement membrane prevents medium to large proteins (e.g. globulins) from crossing.

Table 1: Agents causing mesangial contraction and relaxation

Contraction	Relaxation
Angiotensin II	ANP
Endothelins	Dopamine
Vasopressin	PGE_2
Noradrenaline	cAMP
PAF, PDGF, TXA_2, PGF_2, Histamine, Leukotrines C&D	

Tubule

Proximal convoluted tubule:

- Single cell layer of cuboidal cells, with brush border on luminal side (microvilli).
- Cells interdigitate and have apical tight junctions.
- Lateral intercellular spaces at the base.
  Lateral intercellular spaces are the sites where substances like sodium and glucose are pumped out into the interstitial space after reabsorption into the tubular cell.
- Many mitochondria (many active processes).

Reabsorption of 60-70% of water and solute. Aquaporin-1 in apical membranes act as channels.
Small proteins and peptide hormones are reabsorbed here by endocytosis.
Secretion of some drugs, urea (also reabsorbed), creatinine, uric acid, ammonia and hydrogen.

Pars convoluta drains into pars recta, which is the first part of the Loop of Henle.

Loop of Henle:

Descending limb – thin segment (squamous cells). Permeable to water via permanent aquaporin-1.
Ascending limb – thick segment (cuboidal cells with no brush border). Impermeable to water. Pumps out sodium and potassium, and chloride follows.
Chloride moves via "leaky" tight junctions between cells.
Numerous mitochondria, invaginated basal portions.
Passes close to afferent and efferent arterioles and forms part of the juxtaglomerular apparatus.

Juxtaglomerular apparatus:

1. Juxtaglomerular cells
   a. Part of afferent arteriole – modified smooth muscle cells.
   b. Contract and relax in response ATP, adenosine and NO released by macula densa.
   c. Secrete renin in response to NO and PG's.
2. Macula densa
   a. Histologically different tubular cells of the ascending loop of Henle (cuboidal cells, with a single non-motile cilium that measures rate of flow of filtrate).
3. Lacis cells near them

Early distal convoluted tubule:

Cells' height is lower than those of the proximal tubule; they have fewer mitochondria.

No brush border – fewer microvilli than proximal tubule. Functions similar to ascending limb of loop of Henle.

Late distal convoluted tubule and Collecting duct:

Formed by coalesced distal tubules.
Empty into the pelvis at the apexes of the medullary pyramids.

1. Principle cells (P cells)
    a. Predominate
    b. Relatively tall
    c. Few organelles
    d. Na reabsorption. (Regulated by epithelial sodium channels and Na-K-ATPase; aldosterone stimulates their formation.)
    e. Vasopressin-mediated water reabsorption. (Aquaporin-2 is inserted into the apical membrane in response to vasopressin; interstitial hyperosmolarity in the medulla drives water movement).
2. Intercalated cells (I cells)
    a. Also found in distal tubules
    b. More microvilli, mitochondria, vesicles
    c. Acid secretion and bicarbonate transport.
        i. Aldosterone increases secretion of acid by a H^+ translocating ATPase. The number of H^+ translocating ATPase pumps can be increased by incorporation of ATPase-containing vesicles into the luminal membrane of the cell.
        ii. Band 3 is an anion exchange protein, found in the basolateral cell membranes, that functions as chloride-bicarbonate exchanger.

About 10% of water filtered (i.e. 15-18 l per day) reach the collecting ducts. Here, vasopressin controls the reabsorption: almost all water, or no water at all, can be reabsorbed, depending on hydration status.

Type I medullary interstitial cells:

Secrete PGE_2

Prostaglandin secretion by:

- Type I medullary interstitial cells (PGE_2)
- Cells in the collecting ducts (PGE_2)
- Arterioles and glomeruli (PGI_2 and other)

BLOOD VESSELS

Renal artery – segmental artery – interlobular arteries – arcuate artery – cortical radiate artery –

Afferent arteriole
Short, straight.

Glomerulus
Multiple branches of afferent arteriole.
The only capillaries in the body that drain into an arteriole.

Efferent arteriole
Coalesced glomerular capillaries.

Peritubular capillaries
Multiple branches from efferent arteriole.
Different efferent arterioles may supply different tubular systems via branching vessels.
Technically a portal system is formed.

Interlobular veins

Hydrostatic pressure in glomerulus:

The relatively high hydrostatic pressure in the glomerulus is generated by:
- Short straight anatomy of afferent arteriole
- Relatively high resistance in efferent arterioles

As blood pressure (BP) falls, autoregulation will maintain glomerular blood flow (and therefore glomerular filtration rate (GFR)). When BP falls below the limits of autoregulation, the filtration fraction (GFR relative to glomerular plasma flow) can increase by contraction of the efferent arteriole, providing some protection of GFR. Contraction of the afferent or efferent arterioles decreases tubular blood flow.

Tubuloglomerular feedback:

- Macula densa senses change in rate of flow through ascending loop of Henle and early distal tubule.
- Constriction of AFFERENT arteriole causes inverse change in GFR.

Vasa recta:

Cortical nephrons' tubules only have a peritubular network of capillaries (no vasa recta).
Juxtamedullary nephrons (20-30% of nephrons) have long loops of Henle. The medullary efferent arterioles form both peri-capillary tubules and vasa recta, with the latter running next to the long loops of Henle.
These make hairpin loops next to the loops of Henle.

1. Descending vasa recta
    a. Non-fenestrated endothelium
    b. Facilitated transporter for urea
2. Ascending vasa recta
    a. Fenestrated endothelium
    b. Conserves solute

The renal capsule is thin, but tough. Pressure will increase if the kidney gets oedematous.

INNERVATION

Sympathetic from lower thoracic and high lumbar supply. Mainly supplies:
- Juxtaglomerular apparatus – causes renin secretion (Beta1) [mild stimulus]
- Proximal and distal tubules – causes Na reabsorption [further stimulus]
- Afferent and efferent arterioles
- Blood supply – decreases, GFR decreases [intense stimulus]

Afferent
- Same dermatomal distribution as sympathetic supply
- May mediate reno-renal reflex (increase in one kidney's urethral pressure decreases the sympathetic tone in the other kidney, prompting an increase in Na and H_2O excretion.)

Parasympathetic via vagus.

Autoregulation is not dependent on innervation.

There is dense noradrenergic innervation to the thick ascending loop of Henle.

Hyper- and Hyponatraemia

Dr Howard Radford

Private Practice
Lecturer- Dept of Anaesthesia
University of the Witwatersrand

Disclaimer
These notes have not been peer reviewed. Please refer to appropriate text books and journal articles.

Sodium and water are inextricably linked in the human body. Disorders in their homeostasis often occur in tandem and are ubiquitous. Hyponatraemia and hypernatraemia are common findings in the inpatient and outpatient settings. They are associated with an increased risk of morbidity and mortality. Sodium is the most common cation in the extracellular fluid. Normal concentration of Sodium ranges 135 mmol/l to 145 mmol/l Hypernatraemia is defined as sodium greater than 145 mmol/ whilst Hyponatraemia is defined as a sodium of less than 135 mmol/l. To understand the pathophysiology of hyper and hyponatraemia, it is important to have a knowledge of the regulation of both water and sodium by the body.

Physiology of water and sodium

Water

Total body water varies with gender, age, total body fat and hormonal status. In a normal adult male, water constitutes 60% of total body weight [TBW]. [Correction factors to estimate water volume as % of TBW: New-born 80%; Infant 70%; Paediatric 60%; Male, adult 60%; Female, adult 50%; Male, elderly 50%; Female, elderly 45%]. In adults, fluid is distributed intracellular fluid 40% of TBW and extracellular fluid 20%TBW [i.e. Intracellular water 2/3 total body water and extracellular fluid 1/3 total body water]. Most of the extracellular fluid (ECF) is found in the interstitial space i.e. 13% of TBW and 7% of TBW is found in the circulation (blood and plasma). In neonates because of a smaller mass 55% is found in the ECF.

Water generally diffuses freely across the cell membrane. The movement of water across the membrane is governed by the number of osmotically active particles on either side of the membrane (Osmolarity mmol/l, osmolality mmol/kg). Fluid flows from a low to a high osmolality until equilibrium is reached. The pressure required to prevent the movement of fluid from one side to the other across a membrane is the osmotic pressure. In the extracellular compartment sodium (Na^+), chloride (Cl^-), glucose and are the major osmotically active particles. The osmolality can be calculated using a simple equation $2[Na^+] + [2K^+]$ + glucose + urea. Sodium is the most important determinant of ECF volume. Urea and other small molecules such as ethanol distribute rapidly and evenly across the membrane so while they contribute to osmolality they do not affect the movement of water. The effective osmolality [or tonicity] is thus $2[Na^+] + [2K^+]$ + glucose. The osmolality is more accurately measured in the laboratory using a technique that measures either the depression of the freezing point or boiling point of water. The normal osmolality is about 280 - 290 mosmol/l. To determine the effective osmolality urea must be subtracted from the measured value.

Both water and electrolytes move easily across the capillary membrane whilst only water moves freely across the cell membrane in the short term.

Regulation of osmolality is predominantly based on the hypothalamus monitoring and adjusting plasma osmolality via the secretion of antidiuretic Arginine vasopressin (AVP) (antidiuretic hormone (ADH)) which reduces renal water excretion. AVP binds to the V2-receptor in the collecting duct. This promotes movement of aquaporin 2 to the apical membrane and passive water reabsorption to the hypertonic medullary interstitium. If osmolality increases by a small amount, AVP is secreted to retain body water and lower serum osmolality. (An increase in osmolality will also increase a sense of thirst and increase water intake). Conversely, if a patient's osmolality falls, AVP secretion is inhibited and free water is excreted to raise serum osmolality.

Vasopressin secretion is stimulated when plasma $[Na^+]$ increases. Vasopressin release can also be stimulated by a reduced effective circulating volume via low pressure atrial stretch receptors, stress,

pain, nausea, vomiting, pregnancy, drugs (Isoproterenol Nitroprusside Acetaminophen Beta-2 agonists, Chlorpropamide, Clofibrate, Cyclophosphamide, Epinephrine, Lithium, Morphine (high dose), Nicotine, NSAIDs, Prostaglandins, Tricyclic Antidepressants, Vincristine), Acetylcholine Angiotensin II, Bradykinin and exercise. Vasopressin may be reduced by atrial tachycardia, left atrial distension, Norepinephrine, swallowing and drugs (Alpha-adrenergic agonists, Carbamazepine, Clonidine, Ethanol, Glucocorticoids, Morphine (low dose), Phenytoin, Promethazine).

Volume is regulated most importantly by the stimulation of the renin-angiotensin system in the kidney. When intravascular volume falls, the renin-angiotensin system is stimulated, and aldosterone is released from the adrenal gland, resulting in increased reabsorption of sodium in exchange for increased excretion of potassium and hydrogen. The increased sodium reabsorption will cause more water to also be reabsorbed by the kidney. If too much circulating volume is sensed by the atria, natriuretic peptides are released, resulting in a diuresis. Angiotensin II also stimulates the thirst centres.

Sodium

Sodium is the most prevalent cation in the extracellular fluid. This is maintained by Na^+ / K^+ pumps across the cell membrane. The total body sodium is therefore proportional to ECF volume. Sodium homeostasis is primarily restricted to the extracellular space. Despite great variation in the intake of both sodium and water, close control of serum sodium is maintained via control of the excretion of water and sodium by the kidney and thirst. Over 99% of the sodium filtered by the kidney is reabsorbed in the proximal tubule and loop of Henle. This reabsorption occurs at a relatively fixed rate, regardless of total body sodium. It is the smaller proportion of sodium, reabsorbed in the distal tubule and collecting ducts that exert the most influence on total sodium balance. This is regulated by the renin-angiotensin-aldosterone system. Thirst is stimulated by an increase of a few percent in plasma [Na^+] and a decrease in the effective circulating volume [part of the extracellular volume (ECV) that effctively perfuses the tissue]. Changes in Na^+ will result in alteration in osmolality and thus fluid movement between the ECF and the ICF. Recent experimental work suggests that sodium may be stored in tissues such as skin and muscle and may be regulated by macrophages. The concept of extrarenal regulation of sodium homeostasis provides new avenues for the preclinical and clinical research

Hyponatraemia

As sodium and its accompanying anions are the major effective plasma solutes in the ECF, it is common to for low sodium to level to exist with low, normal or high osmolality see figure 1 Further it may be useful to classify hyponatraemia based on fluid status. Traditional classifications according to volume status are notoriously difficult to handle in clinical practice. Following a simple algorithm for the diagnosis and treatment of hyponatraemia has been shown to be associated with improved outcomes. See figure 1. Measure sodium and plasma osmolality, assess volume status and determine spot urine sodium and osmolality.

Hypo-osmolar hyponatremia
“True hyponatraemia” is regarded as a low sodium level in the presence of hypoosmolality. This is because sodium in the ECF and potassium in the ICF (along with their associated anions) determine osmolality, with water moving freely between fluid compartments, to maintain the same osmolality between compartments. As a result, plasma hypo-osmolality, indicates a relative excess of water to sodium, regardless of volume status. It is an oversimplification to regard hypo-osmolar states as a product of either water excess or solute depletion, as often both are involved.

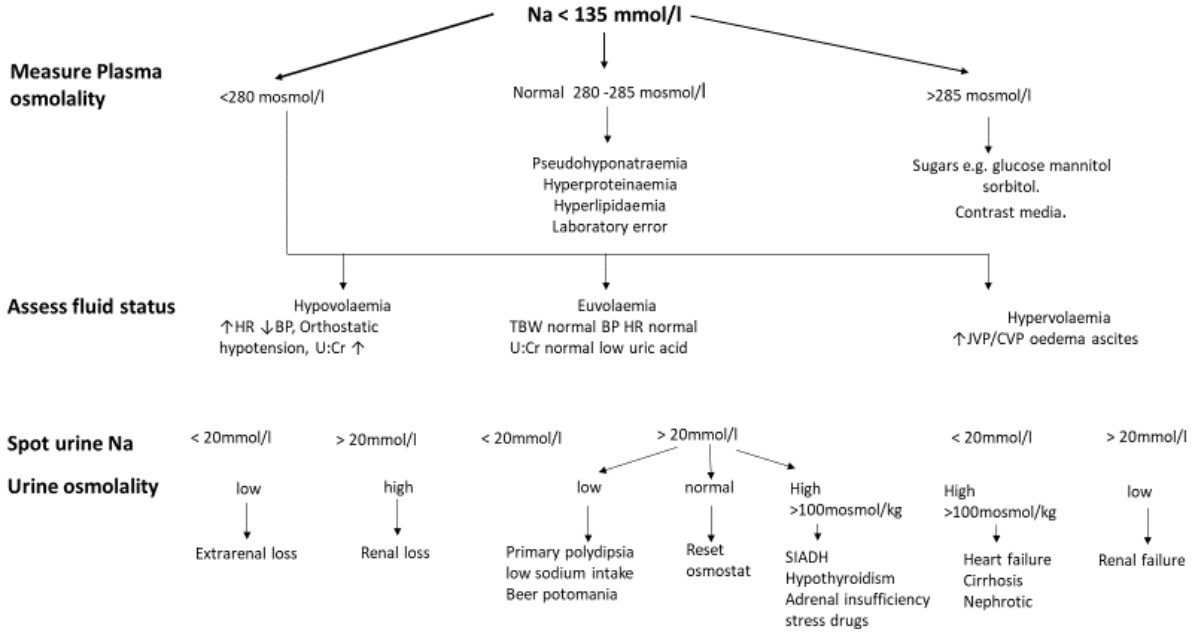

Figure 1
Hyponatraemia

Hypo-osmolar hypovolaemic hyponatraemia
The total body water and total body sodium are both low, but there is disproportionate loss of sodium compared with water. This is a result of the increased ADH secretion seen in hypovolaemic states causing increased water reabsorption. Hyponatremia is often compounded by thirsty patients consuming hypotonic fluids at a level inadequate to try to restore circulating volume.
Sodium loss can be renal or extra- renal. A urinary sodium level below 20mmol/l is suggestive of an extra-renal cause. Extra renal causes may be due to gastrointestinal loss (common), exercise (also commonly seen in people working in hot conditions), burns, trauma, and pancreatitis. A urinary sodium concentration greater than 20 is due to renal causes, diuretic excess, renal failure, salt wasting nephropathy, aldosterone deficiency, chronic pyelonephritis, nephrocalcinosis, proximal renal tubular acidosis and ketonuria.

Hypo-osmolar euvolaemic hyponatraemia
The syndrome of inappropriate ADH (SIADH) is the most common cause of euvolaemic hyponatremia and has numerous causes. If SIADH is suspected, it can be useful to measure urine osmolality. A urine osmolality >100 mOsm/kg in the presence of hyponatraemia reflects inappropriate antidiuresis. Other causes include glucocorticoid insufficiency hypothyroidism and drugs e.g. SSRis

Hypo-osmolar hypervolaemic hyponatraemia
This is a situation characterised by a paradoxical increase in total body sodium, but a simultaneous and proportionally larger increase in total body water leading to a dilutional hyponatremia. This reduction in water excretion is secondary to either an excess of AVP secretion or renal impairment limiting the maximal excretion of free water. The increase release of AVP may be due a decrease in arterial effective volume this is seen in nephrotic syndrome, congestive cardiac failure (CCF) and cirrhosis. Such patients commonly have a raised spot urine sodium and osmolality. In renal failure patients are unable to reabsorb sodium and have water retention due decrease filtration. They will often have an increase in urine sodium and often decrease urine osmolality.

Normo-osmolar hyponatraemia
Hyponatraemia occurring without hypo-osmolality is referred to as pseudohyponatraemia. Pseudohyponatraemia can occur with a normal or elevated serum osmolality. Pseudohyponatraemia with normal serum osmolality occurs when grossly elevated levels of lipids or proteins lead to an artificial apparent decrease in measured serum sodium. This is because sodium normally distributes in the aqueous phase of plasma which accounts for 93% of the plasma volume. A correction factor for whole plasma can be rendered incorrect if the non-aqueous phase is increased due to hypertriglyceridaemia or paraproteinaemia. The use in laboratories of direct ion-sensitive electrodes

instead of a flame photometer eliminates this potential error. Glycine often used in urological procedures and mannitol are unable to cross the cell membrane and remains in the plasma resulting in movement of water from the intracellular space into the ECF thus causing a decrease in sodium concentration and an increase in the effective osmolality. Glucose normally diffuses freely into cells but when insulin is deficient, glucose is effectively confined to the ECF. When the concentration of glucose rises, water moves across the membrane from inside to outside the cell, dehydrating the cell, and causing a dilutional hyponatraemia. In diabetic ketoacidosis, the "true" corrected serum sodium can be estimated from the formula: [Na+] corrected= [Na+] measured + {(glucose-5.6) x 0.288}. or $[Na^+]$ is reduced approximately 0.4 mmol/l per mmol/l increase in P-[Glc] eg. If the patient's measured glucose is 20mmol// and the measured Na^+ is 122 mmol// then the true Na^+ is approximately 127 mmol//

Hyper-osmolar hyponatraemia
An increase in sugars eg glucose mannitol and sorbitol and radio contrast media cause an increase osmolality and cause an increase in fluid influx into the ECF from the ICF resulting in a decrease in Sodium concentration.

Hypernatraemia

Hypernatraemia is caused by net water loss (increased loss or decreased intake) or, rarely, sodium gain. Patients at increased risk include those with an impaired thirst mechanism or restricted access to water (e.g., those with altered mental status, intubated patients, infants, older adults). See figure 2

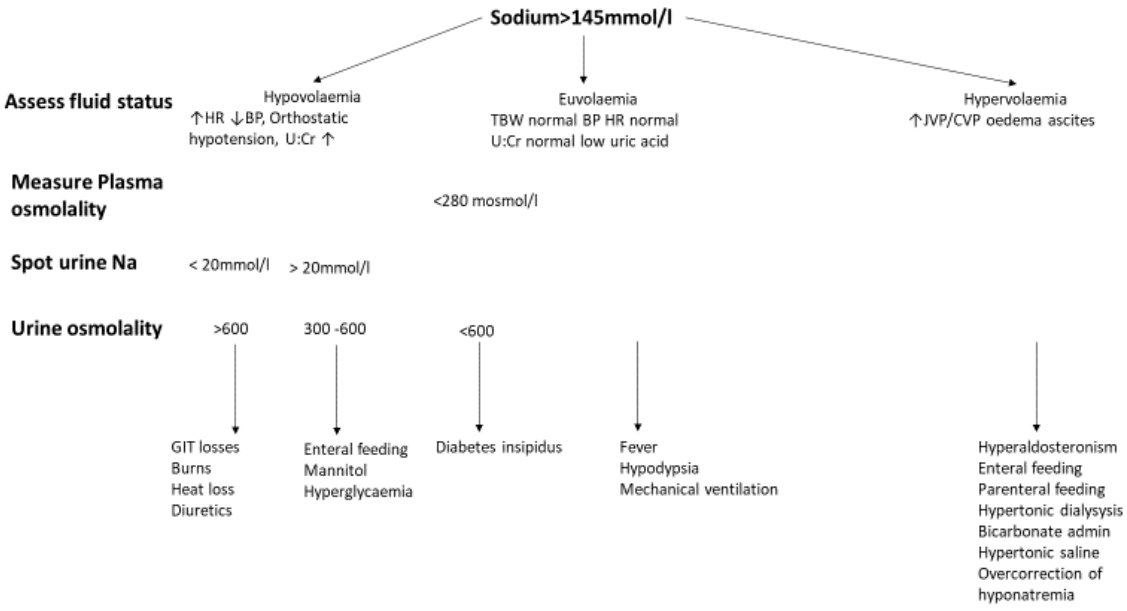

Figure 2
Hypernatraemia

Treatment

Both Hyponatremia and hypernatraemia cause significant morbidity and mortality. Both require urgent management. Too rapid correction may result in significant brain injury. Whether treating hyponatraemia or hypernatraemia, the concentration of sodium should not change by more than 8 – 10mmol/l per 24hours.

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Available on request

Suggested article.
Braun M M, Barstow C H, Pyzocha N J. Diagnosis and Management of Sodium Disorders: Hyponatremia and Hypernatremia Am Fam Physician. 2015;91(5):299-307

Volatile Pharmacokinetics

Dr Ettienne Coetzee

Dept of Anaesthesia & Perioperative Medicine
University of Cape Town

Preface

Volatile anaesthesia has been in use for nearly two centuries. The accuracy, predictability and safety has changed dramatically from the first case report in 1842, where the patient inhaled ether from a towel[1], to state of the art anaesthetic advisory systems with target controlled administration and complex mathematical predictions accounting for additive and/or synergistic pharmacological interactions. This refresher contains a summary of the current recommended literature and aims to illustrate the basics of volatile pharmacokinetics, its dependant influences and its relevance to the anaesthetist.

Introduction

Knowledge on the physiology of cellular signalling brought about our understanding and appreciation of receptors, the ligands that bind to receptors and our ability to interfere with these mechanisms.[2] Various theories exist describing the mechanism of action of inhalational anaesthetics (IA), although the exact mechanism still elude us. Current research explores the possibility that IA have specific receptor or protein interactions that result in their clinical (or pharmacodynamic) effects. The likely target receptors are *tandem pore K^+channels, voltage-gated Na^+channels, N-Methyl-D-aspartate (NMDA) receptors and pentameric ligand-gated ion channels* (which include *glycine receptors* and *γ-aminobutyric acid receptors*).[3] For IA to exhibit an effect on target proteins, they require a relative high ambient concentration, indicating some degree of non-specificity in their binding. Binding of IA to a receptor can either potentiate or inhibit its function, depending on the specific receptor and the binding site on the receptor.[3] The details fall outside the scope of this chapter and the reader is directed to some of the references for more on this topic.[3,4] To achieve these pharmacodynamic target end-points, delivery of the IA to the target organ (effect site, likely the brain and/or spinal cord) must be achieved. The knowledge of delivery, absorption, distribution and removal of pharmacological agents is one of the chief requirements of the anaesthetist. A thorough understanding of the pharmacokinetics is therefore paramount.

Delivery of inhalational anaesthetics

To fully appreciate the pharmacokinetics (PK) of IA, one must understand how the delivery of IA takes place. This chapter assumes basic familiarity of the reader with anaesthetic breathing circuits, the concept of fresh gas flow, vaporisers, rebreathing circuits (such as the circle system) and carbon dioxide absorbers (see *figure 1*). Non-rebreathing circuits rely on high fresh gas flows (at, or above alveolar ventilation) to avoid rebreathing of carbon dioxide. They currently have limited use in modern anaesthesia. Since wash-in kinetics apply to all circuit types *to some degree*, the specifics of circle system wash-in kinetics can be applied to non-rebreathing circuits, with the provision that their fresh gas flows are appropriately elevated. Once fresh gas flows are reduced to allow for rebreathing, the circle system exhibits unique kinetics. To avoid confusion, the following section will exclusively discuss the kinetics of circle systems.

Background

After the introduction of calibrated vaporisers, the delivery of inhalational agents became more predictable and safe (no more wrapping the patient's head in an ether soaked towel!). At that point in time, the delivery of high fresh gas flows (FGF) ensured predictable inspired anaesthetic amount at the cost of significant waste. The ability to lower FGF to below alveolar ventilation was made possible using the circle system by allowing rebreathing of expired gas, with its additional requirement: the carbon dioxide absorber (see *figure 1)*. Before the advent of reliable gas analysers, only well-seasoned anaesthetists could reduce FGF to improve economy. Admixture of unknown amount of exhaled vapour resulted in a "best guess" scenario, since the accurate calculation of total vapour and oxygen requirements at low FGF was complex and laborious. The arrival of modern breath-by-breath

gas analysis systems significantly simplified anaesthetist-vaporiser interactions. Additionally, modern volatile agents are leaps closer to the "perfect" inhalational agent, with rapid induction- and emergence times as well as improved context-sensitive half-times. These advances have brought about a complacent attitude towards the pharmacokinetics of inhaled anaesthetics. Understanding the pharmacokinetics will not only provide the reader with enhanced insights into the differences between specific agents, but also on its utility towards safe and predictable pharmacodynamic application, as well as pharmacoeconomic implications.[5]

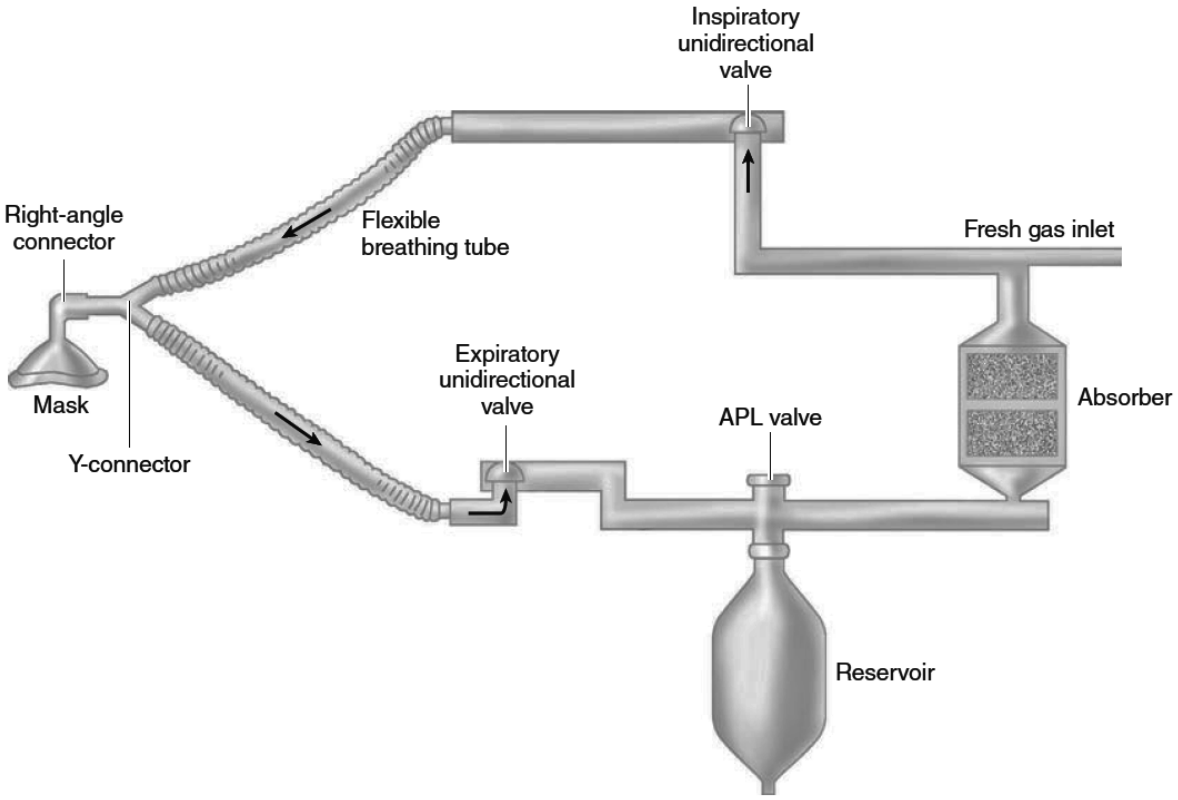

Figure 1 – The Circle Breathing System
APL, adjustable pressure leak;
Butterworth JF, Mackey DC, Wasnick JD. Morgan & Mikhail's Clinical Anesthesiology. McGraw-Hill Education; 2013. page 37.

Table 1
Different definitions of decreased fresh gas flow[6]

Definition	Fresh gas flow (mL/min)
Metabolic flow	**~ 250**
Minimal flow	**250 - 500**
Low flow	**500 – 1000**
Medium flow	**1000 – 2000**
High flow	**2000 – 4000**
Open circuit flow	**> 4000**

Circuit kinetics

The pharmacodynamic activity of an anaesthetic gas depends on its thermodynamic activity in vivo (the likelihood of drug-receptor interaction). This is governed by its *partial pressure*. The partial pressure is usually reported as the fraction (or percent) in relation to atmospheric pressure. It is useful to consider the effect of altitude on this concept.[7] The properties of the IA have been illustrated using *partial pressures* wherever possible. This can be converted to fraction by dividing by the barometric pressure. See *table 2.*

Table 2
Physical characteristics and properties of inhalational anaesthetics and other gases[4,8,9]

Name	MW	BP (^oC)	SVP(kP-$_a$) @ 20°C	λ_{BG} @ 37°C	λ_{BB} @ 37°C	λ_{OG} @ 37°C	Metabolism (%)	$MAPP_{50}$ (kP_a)[10]	$MAPP_{awake}$ (kP_a)[10]
N_2O	44.0	-88.5	5200	0.47	1.1	1.3	None	105	69.7
Xenon	131.3	-108.1	3200[11]	0.114	0.12[12]	1.8[13]	None	~72[8]	33.0[14]
Desflurane	168	23.5	88.3	0.42	1.3	19	0.02	6.5	2.24
Sevoflurane	200.5	58.5	21.3	0.65	1.7	47-54	3	1.9	0.65
Isoflurane	184.5	48.5	33.2	1.46	1.5	90.8	0.2	1.2	0.41
Halothane	197.4	50.2	32.3	2.4	2.7	197	20-50	0.77	0.42

MW molecular weight; BP boiling point; SVP saturated vapour pressure; λ_{BG} blood-gas partition coefficient; λ_{BB} brain-blood partition coefficient; λ_{OG} oil-gas partition coefficient $MAPP_{50}$ minimum alveolar partial pressure to prevent 50% of patients (aged 40 years and at normal temperature) from purposeful movement during a standardised painful stimulus; $MAPP_{awake}$ minimum alveolar partial pressure at which 50% of patients (aged 40 years and at normal temperature) will respond to verbal command;

Circuit wash-in kinetics represent an example of bulk transfer exchange. Bulk transfer exchange is an example of first-order kinetics, commonly found in pharmacokinetics, since it relies on concentration- or partial pressure gradients to drive movement of substances.

*A brief look at First-Order Kinetics – Remember the **concepts**, not the **formulas***
First-order kinetics describe the movement of a *constant proportion* of substance *per unit time*. To assist the reader with the origin of first-order kinetic equations, we will briefly consider a simple example to illustrate the background of these calculations. Consider the following example:

The elimination of drug A over time was found to occur as follows: for every minute, 10% of the drug was removed from the body. If the initial amount of drug A in the body was 100 mg, it would mean that after minute 1, 10% would be removed. This would result in 10 mg being removed with 90 mg remaining. After minute 2, another 10% *of 90 mg* will be removed. Now 9 mg has been removed with 81 mg remaining. After minute 3, another 10% will be removed. At this point, 10% of 81mg is 8.1 mg, thus after minute 3, 72.9 mg will remain in the body. If we continue the calculations for the first 30 minutes, we can see the following graph (*figure 2)*.

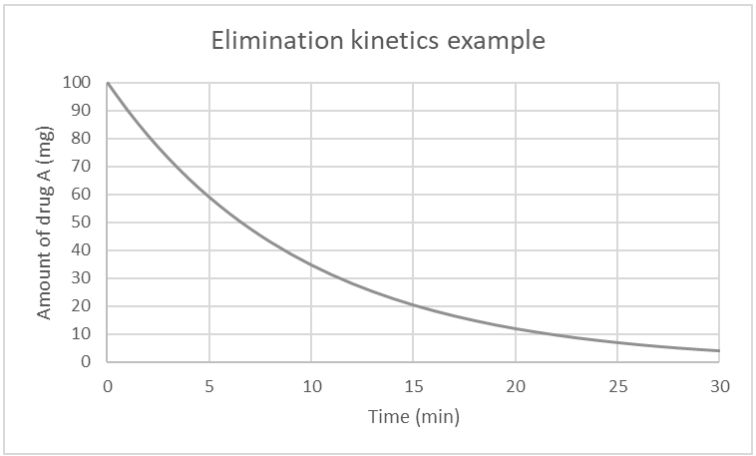

Figure 2 - Example of elimination first-order kinetics

The resulting curve resembles a non-linear decay in amount of drug. This curve is difficult to represent mathematically without the use of advanced calculus. To simplify the curve, we can plot the *y-axis* on a *natural logarithmic scale* ($log_e y$) and convert the curve as follows (*figure 3*).

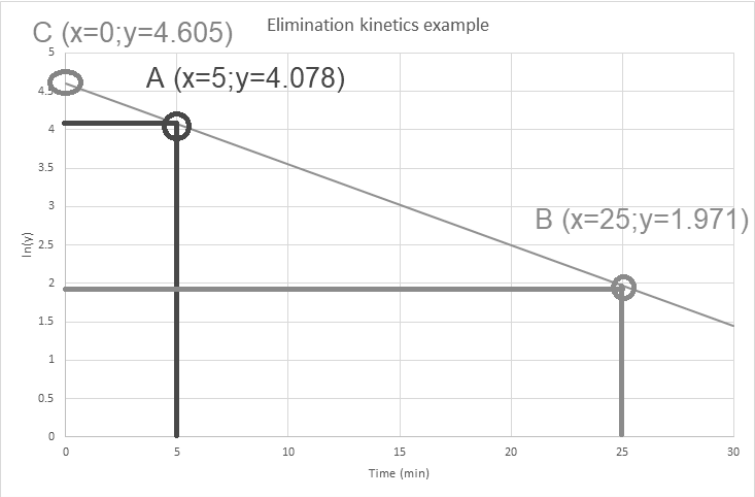

Figure 3 - Natural log scale on the y-axis with two points, A, B and y-intercept C

Once we change the *y-axis* scale, the curve becomes a straight line. Now it represents a line we can easily transform into a mathematical equation: the equation of a straight line.

$$y = mx + c$$

Where *m* represents the slope of the curve and *c* the *y-axis* intercept. However, since we have changed the *y-axis* to *natural logarithm* scale, we have to add this into our equation as follows:

$y = mx + c$ now becomes:

$\log_e y = mx + \log_e c$ (remember: *c* is the *y-axis* intercept, which is in *natural logarithm* scale)

The slope can now be calculated by reading off the co-ordinates of points A and B and calculating the change in *y* divided by the change in *x,* and the equation solved.

The *natural logarithm* merely represents the *logarithm to the base* ***e***, where ***e*** is a constant referred to as *Euler's number*. Therefore, you will find *Euler's number* in the calculations of first-order kinetics, a common mathematical finding in pharmacology, physiology and the natural world. Using this constant in exponential equations, successfully describes many occurrences in nature, one such example being pharmacokinetics. For interest's sake, *Euler's number* is a constant (also called *Napier's number*) and can be calculated as:

$$e = (1 + \frac{1}{n})^n = 2.7182818284 \ldots$$

You might recall seeing this constant in other pharmacokinetic equations, such as calculating the plasma concertation after a single intravenous bolus dose:

$$C_p(t) = C_o \boldsymbol{e}^{-kt}$$

where C_o is the initial plasma concentration and *k* the elimination rate constant (similar to *m* in the above example). Time, represented by *t*, will be the time elapsed since the bolus dose. In other words, this equation can calculate the plasma concentration at an exact moment in time.

As mentioned, the slope of the curve will represent the *rate constant,* which in the above example is *negative*, since there is decay of drug. This will be *positive* when we consider *wash-in* kinetics, since we will have an increase in gas partial pressure over time.
The above example is slightly oversimplified, but it serves merely to illustrate the concept of first-order kinetics. These equations are not to be learned off by heart, but serve as a guide to the understanding of how physical occurrences can be represented mathematically. Like Newton used mathematical terms to calculate velocities of moving objects, we can calculate movement of drug.

From vaporiser to circuit – Basics of circuit wash-in kinetics

Fresh gas flow

The amount of oxygen (or N_2O) being delivered will depend on the ratio of oxygen to air (or oxygen to N_2O). For example, 2 L/min of O_2 plus 4 L/min of N_2O will deliver a total FGF of 6 L/min of which 33.8 kP_a will be O_2 and 67.6 kP_a will be N_2O. In terms of fractions, 33.3% will be O_2 and 67.7% will be N_2O at 6 L/min total FGF at sea level (with barometric pressure of 101.325 kP_a). Calculating the fraction of O_2 or N_2O when only those two gases are used as FGF, is easy, when one is using air and O_2, it becomes more complex, since air also contains ~21% O_2. A simplified equation to determine the fraction of delivered O_2 during O_2 and air delivery, is:

$$F_{iO_2} = \frac{\dot{V}_{O_2} + (\dot{V}_{air} \times F_{iAIR})}{F\dot{G}F_{total}}$$

Where $\dot{V}_{O_2}$ is the flow rate of oxygen, $\dot{V}_{air}$ is the flow rate of air and $F\dot{G}F_{total}$ is the total fresh gas flow (the sum of oxygen- and air flow), all in L/min. F_{iAIR} is the fraction of O_2 in air, which is ~0.21. To convert F_{iO_2} to partial pressure, simply multiply the result by the barometric pressure.

Circuit kinetics[4]

To determine the pharmacokinetics of the circuit alone, we need to consider what will influence the rate of change in the circuit over time. In other words, what are the things responsible for changing the content of the circuit over time. The movement of any fluid requires a *pressure gradient* across the fluid (whether it be gas or liquid). In the circuit, we can illustrate this pressure gradient (ΔP_{circ}) as the difference between the partial pressure of gas in the FGF (P_{del}, since this is the partial pressure of gas being *delivered* to the circuit) and the partial pressure of gas currently present in the circuit (P_{circ}). Thus, this pressure gradient can be mathematically represented as:

$$\Delta P_{circ} = P_{del} - P_{circ}$$

ΔP_{circ} represents the change in pressure (with the unit of *kP*$_a$ of a specific gas, for example). However, this equation represents no utility to us, as it does not account for the passage of time. In other words, this equation only represents a singular moment in time where we know all of the values on the right side of the equation. To determine the *rate* of change *per unit time* we need to add *time as a denominator* to the above equation. To do so, let us look at what other variables we have in the circuit: we have the FGF (which is in $\frac{volume}{time}$, usually $\frac{L}{min}$) and of course, the total circuit volume (usually in *litre*). If we divide the FGF by the volume of the circuit, we do the following:

$$\frac{F\dot{G}F}{V_{circ}} = \frac{\frac{litre}{min}}{litre} = \frac{litre}{min} \times \frac{1}{litre} = min^{-1} = \frac{1}{\Delta t}$$

We now have a unit of time as the denominator. $\frac{F\dot{G}F}{V_{circ}}$ has a unique term. This relationship is also called the *circuit time constant* notated as τ (tau) with unit of min^{-1} (or *per minute*).

By multiplying tau with the pressure differential (ΔP_{circ}), we can now calculate the change in partial pressure *over time*, in other words: *the rate of change over time*:

$$\frac{\Delta P_{circ}}{\Delta t} = \frac{F\dot{G}F}{V_{circ}} \times (P_{del} - P_{circ}) = \frac{change\ in\ pressure}{change\ in\ time}$$

This equation, represents the differential equation to solve the *circuit pharmacokinetics*.

When the vaporiser is activated, volatile will be delivered to the circuit in gaseous phase. The volume being delivered is determined by the product of the vaporiser setting and the total fresh gas flow being delivered to the vaporiser. Most vaporisers display delivery of vapour in terms of fraction of fresh gas flow (% v/v). However, since most vaporisers utilise a variable bypass chamber (with the exception of the desflurane vaporiser) and therefore end up delivering varying dilutions of the specific agent's

saturated vapour pressure (which is only affected by *temperature*), the vaporisers actually deliver a specific *partial pressure* of the agent, that is ***independent of barometric pressure***.[7] We can therefore integrate the *partial pressure* of delivered volatile into an equation to determine the amount of gaseous-phase anaesthetic being delivered over time:

$$V_{del}(t) = P_{del} \times F\dot{G}F \times t$$

Where $V_{del}(t)$ is the volume of gaseous anaesthetic, mixed with the carrier fresh gas at time *t*. P_{del} is the partial pressure of anaesthetic being delivered per unit time and *t is* a specific amount of elapsed time.

Over time the difference between P_{del} and P_{circ} will progressively decrease, as wash-in takes place and this tells us that the rate of change will progressively decrease over time (as demonstrated by the wash-in curves later). We can therefore deduce that this pressure differential impacts wash-in kinetics: if it is large (big difference between P_{del} and P_{circ}), the *rate* of wash-in is high; when P_{del} and P_{circ} are almost equal, this difference approaches zero and therefore the wash-in rate approaches zero – in other words, equilibrium is imminent.

Therefore, if we consider the circuit alone, the circuit wash-in characteristics are determined by:
1. *the fresh gas flow* (FGF) – total gas volume delivered by the fresh gas inlet (O_2, air, anaesthetic vapour with or without N_2O) per unit time, usually in *litres per minute*
2. *the total volume of the circuit* (V_{circ}) – including circuit tubing, CO_2 absorbent canister and reservoir bag or ventilator bellows/piston, usually in *litres*
3. *the amount of gas or volatile delivered (P_{del})* – if we consider the volatile agent, this will be determined by the vaporiser setting (which is usually represented as a fraction) but the same principle will apply to other gases being washed in – which is usually represented either as a fraction (%) or *partial pressure (kP$_a$ or mmHg)*.

Let us look at examples to help us understand the influence of these variables.

At a constant circuit volume and FGF, the influence of variable amount delivered (P_{del}) is shown in *figure 4.*

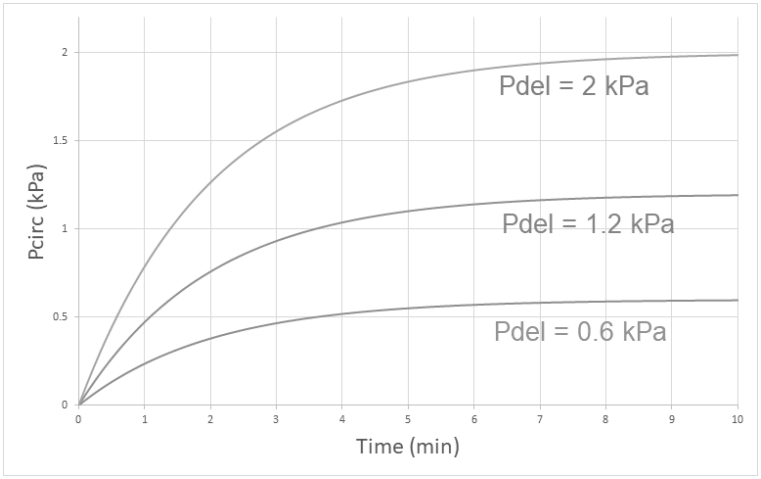

Figure 4 - Influence of variable Pdel on wash-in curves

Notice that for higher delivered amount of anaesthetic, the wash in curve has a steeper initial curve, but that they have similar shapes, in other words, they equilibrate at similar times with their respective P_{del}. At time = 1 minute, all three curves will be at the same fraction of their respective P_{del}. The same applies for time = 10 min, where all three curves will be almost equal to their respective P_{del}. Two facts can be deduced from *figure 4*: at constant FGF and circuit volume, the *rate of change* for a given P_{del} will be similar; eventually the P_{circ} will equilibrate with P_{del} and for a constant *Vcirc* and *FGF*, that will occur at the same point in time, hence we call the $\frac{V_{circ}}{F\dot{G}F}$ the *circuit time constant (tau)*. The clinical utility of this is part of every-day anaesthetic practice: if we keep the FGF constant, to expedite induction of anaesthesia, we have to increase the amount of vapour delivered to the circuit by increasing P_{del}. This is sometimes referred to as delivering "*overpressure*". However, at some point we will reach our

target vapour amount and to avoid overshoot, we then have to turn down the vaporiser to just maintain the target amount (in other words, decrease P_{del}). See *figure 5*. Delivering "overpressure" significantly decreases the time to reach our target.

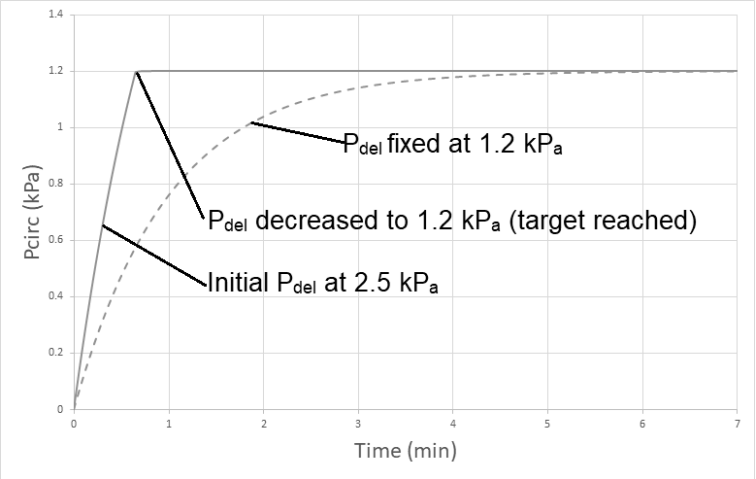

Figure 5 Fixed FGF of 6 L/min in a 6 L circuit with the P_{del} change during wash-in versus fixed P_{del}

Let us consider the opposite, and alter the *circuit time constant* while keeping the P_{del} constant. Firstly, we will keep the circuit volume constant, along with constant P_{del}, while altering the FGF. This results in the following graph (*figure 6*). Three different FGF rates are illustrated (6 L/min, 3 L/min and 1.5 L/min).

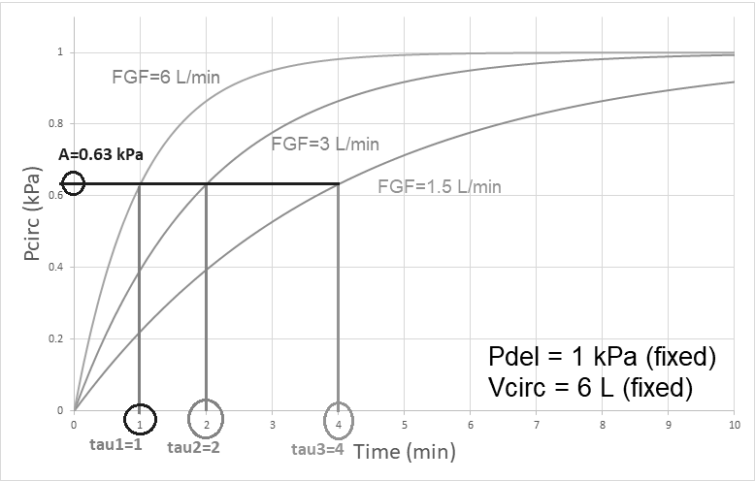

Figure 6 - Fixed Vcirc and Pdel with variable FGF

For *figure 6* the following *circuit time constants* can be calculated for their respective FGFs:

$$\tau_1 = \frac{V_{circ}}{F\dot{G}F_1} = \frac{6L}{6L/min} = 1min$$
$$\tau_2 = \frac{V_{circ}}{F\dot{G}F_2} = \frac{6L}{3L/min} = 2min$$
$$\tau_3 = \frac{V_{circ}}{F\dot{G}F_3} = \frac{6L}{1.5L/min} = 4min$$

From *figure 6* we can deduce the following facts: by increasing the FGF, we can expedite the wish-in time (notice the steep slope of the curve with FGF = 6 L/min). Regardless of the FGF, the circuit will eventually equilibrate at the P_{del}, but this will occur after a longer time for lower FGFs. The $\frac{V_{circ}}{F\dot{G}F}$ relationship, now known as *tau (τ)*, can be used to represent how fast or slow wash in will occur. The higher the number of *tau,* the slower the wash-in. If we plot the time constants on the graph, we can see that after each time constant, the circuit has equilibrated to a similar amount (of ***0.63 kPa***). Since our P_{del} was fixed at 1 kPa in this example, we can therefore deduce that ***after one time constant***

has elapsed, the circuit will have reached 63% of its P_{del} (0.63 kPa of 1 kPa = 63%). Therefore, after one time constant, the circuit will reach 63% of whatever is contained in the FGF, but will also wash-out 37% (100% - 63%) of whatever is already in the circuit. We can also deduce that by *doubling* the FGF, we *half* the time constant. The opposite also applies (see τ_3 versus τ_2 and τ_2 versus τ_1). This applies to all the substances contained in the FGF. Another useful deduction, is that ***after 4 time constants have elapsed, the circuit will be 98% equilibrated***. Again, after 4 time constants have elapsed, only 2% (100% - 98%) of the original circuit content will remain. Thus, the time taken for *near-total* ***circuit wash-in/wash-out*** is approximately $4 \times \tau$. For this reason, during pre-oxygenation and emergence, FGFs should be increased to ≥ minute volume to rapidly alter the circuit content. Finally, we can repeat the above experiment and alter the circuit volume while maintaining fixed P_{del} and FGF. See *figure 7.*

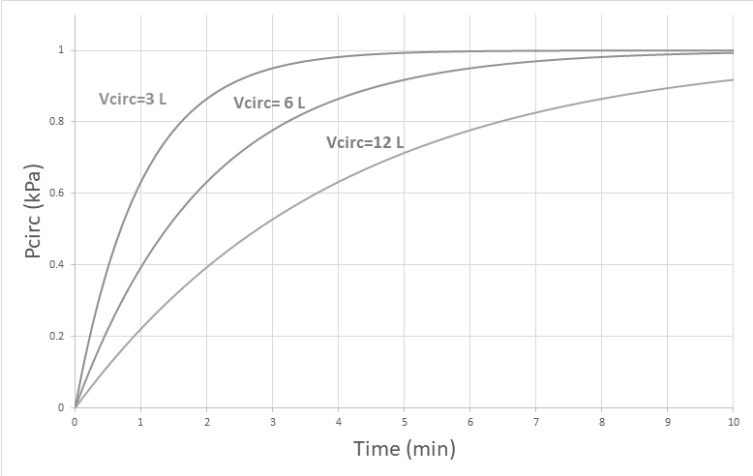

Figure 7 - Variable circuit volumes at fixed FGF and Pdel

Figure 7 shows us how V_{circ} has an opposite effect to wash-in time: increasing V_{circ} results in slower wash-in times. This can have clinical considerations where paediatric patients are connected to a circuit with a large reservoir bag, or in certain remote-site anaesthetic situations where the patient is far from the anaesthetic machine due to radiological interventions or investigations (*interventional neuroradiology or MRI procedures*) resulting in long tubing and therefore large circuit volumes.

Another useful way to represent the circuit time constant (*tau)* is in relation to *circuit wash-in half-time*, or the time taken for 50% equilibration between circuit partial pressure and vaporiser setting (P_{del}). The relationship can be mathematically represented as:

$$t_{1/2circ} = \tau \times \log_e 2 = \tau \times 0.693$$

Therefore, the circuit half-time for a circuit of *7 L and at FGF of 2 L/min* would be:

$$t_{1/2circ} = \tau \times \log_e 2 = \tau \times 0.693 = \frac{7}{2} \times 0.693 = \sim 2.4\ min$$

To reach 98% of the delivered anaesthetic agent as dialled in by the vaporiser would be:

$$4 \times \tau = 4 \times \frac{7}{2} = 14\ min$$

So far, we have only considered *wash-in* kinetics of the circuit. The same physical laws will also govern the wash-out of substances from the circuit. An uncomplicated way of approaching circuit wash-out, is merely to consider that it is the wash-in of another substance, that will replace the current.

In summary, circuit kinetics is determined by the *amount of substance delivered, the flow rate of the FGF and the total volume of the circuit.* For rapid wash-in to occur, a large FGF and/or a small circuit volume should be selected. Changing the vaporiser output can further alter the rate of obtaining a specific target amount and therefore also contribute to altering the wash-in kinetics. Each combination of circuit volume and FGF give a unique *circuit wash-in time constant* called tau (τ) which can be used to predict when wash-in or wash-out will occur. Circuit wash-in or wash-out half-time can be calculated

as $\tau \times 0.693$. To calculate near total wash-in or wash-out (98%): $\tau \times 4$. Similar physical laws govern wash-out of the circuit, with the notable exception that one can only decrease to vaporiser output to zero and not give a *negative* number of vapour to further expedite wash-out, whereas one can give significantly high wash-in pressures with most modern vaporisers.

Kinetics of inhalational agents – connecting the patient to the circuit

Once a patient is connected to the breathing circuit, various other factors initiate a complex cascade of events. We will consider them one by one.

First contact – the lungs[4]

The collective airspace of the lungs includes both dead-space- and alveolar ventilation. Since this volume is not merely an extension of the anaesthetic circuit, but subject to its own filling characteristics, we have to accommodate appropriately to illustrate its unique kinetics, however, the principles remain similar. Once again, we have a *time constant* and a *pressure gradient.* The pressure gradient driving gas into the pulmonary airspace, will be the difference between the circuit- and pulmonary airspace partial pressure $(P_{circ} - P_{pulm})$. Since the pulmonary airspace does not merely extend out of the circuit volume, but rather undergoes cyclical ventilation, called *minute volume*, the time constant driving its kinetics is $\frac{MV}{V_{pulm}}$, where *MV* is *minute volume in litre/minute* while V_{pulm} is the *pulmonary airspace volume* in *litre*. Therefore, pulmonary airspace kinetics can be represented as follows:

$$\frac{\Delta P_{pulm}}{\Delta t} = \frac{MV}{V_{pulm}} \times (P_{circ} - P_{pulm})$$

Note the similarities with the circuit kinetics equation from earlier. Both equations have time constants and pressure gradients. Indeed, they can be added together to simultaneously represent the effects of connecting a patient to the anaesthetic circuit:

$$\frac{\Delta P_{circ}}{\Delta t} = (\tau_{circ} \times \Delta P_{circ}) - (\tau_{pulm} \times \Delta P_{pulm})$$

The second term is *subtracted* from the circuit since it will remove gas from the circuit.

$$\therefore \frac{\Delta P_{circ}}{\Delta t} = \left(\frac{F\dot{G}F}{V_{circ}} \times (P_{del} - P_{circ})\right) - \left(\frac{\dot{M}V}{V_{pulm}} \times \left(P_{circ} - P_{pulm}\right)\right)$$

This equation illustrates the effect of both the circuit kinetics and the pulmonary kinetics on rate of change of the circuit partial pressure over time. If we ignore the circuit-only kinetics for a second and focus on the *second term of the equation*, we can deduce the following:

The pulmonary time constant (τ_{pulm}) is directly proportionate to the *minute volume* ($\dot{\mathrm{M}}\mathrm{V}$) and indirectly proportionate to the *pulmonary airspace* (V_{pulm}). From earlier, we know that a small time constant causes a rapid *rate of change*. In this instance, the rate of change will be to drive gas from the circuit into V_{pulm}. Therefore, a large $\dot{\mathrm{M}}\mathrm{V}$ or small V_{pulm} will result in rapid equilibration between circuit and pulmonary partial pressures. Similarly, the pressure gradient will also impact the rate of change: larger circuit partial pressures will cause large pressure gradients and increase the rate of change $\left(P_{circ} - P_{pulm}\right)$. As P_{pulm} increases over time, this pressure gradient will decrease as will the rate of change, denoting tendency towards equilibrium. Additionally, during wash-out of IA, first P_{del} followed by P_{circ} will approach zero (once the vaporiser is closed and the FGFs increased). Soon P_{circ} will be less than P_{pulm}. This will render the second term *positive*, therefore indicating *wash-out* from the lungs, *toward* the circuit.

Another deduction we can make is that the $\frac{\boldsymbol{MV}}{\boldsymbol{V_{pulm}}}$ ratio (τ_{pulm}) is significantly higher in neonates and children (since they have a relatively higher cardiac output, the *MV* must increase disproportionately when compared to V_{pulm}, to accommodate the higher pulmonary blood flow, since cardiac output and

MV are nearly equal under normal conditions) and they will therefore more rapidly equilibrate their pulmonary airspace.

Summary up to this point
The anaesthetic circuit has its own wash-in kinetics. The wash-in kinetics are dependent on:
a) FGF (higher FGF, smaller τ_{circ}quicker wash-in)
b) Circuit volume (lower volume, smaller τ_{circ}, quicker wash-in)
c) P_{del}, the amount of anaesthetic in the fresh gas flow, which can also be the *vaporiser setting* (higher setting, more inhaled anaesthetic delivered, greater *pressure gradient* $(P_{del} - P_{circ})$ to circuit, quicker wash-in)

Once a patient is connected, the patient's lung compartment adds additional complexity to the kinetics, but with similar dependable variables:
a) Minute volume (higher *MV*, smaller τ_{pulm}, quicker wash-in)
b) Lung volume (lower volume, smaller τ_{pulm}, quicker wash-in)
c) Higher inhaled partial pressure from circuit, higher *pressure gradient into* $\left(P_{circ} - P_{pulm}\right)$ lungs, quicker wash-in.

Alveolar partial pressure and anaesthetic uptake[4,8,9]

According to Henry's law, the amount of gas that will dissolve in a solvent is directly proportional to its partial pressure applied to the solvent. If we consider a cup with a solvent and an amount of gas applied to the solvent, we can deduce that some of the gas will enter the solvent, depending on the gas's specific affinity for the specific solvent. As the gas enters the solvent, it will reduce the applied partial pressure, since some of the gas particles are now in the solvent (less are present in the geseous phase). Simultaneously, some of the dissolved gas particles will spontaneously exit the solvent, however, initially the amount that will exit will be low, since little gas has dissolved. his will again increase the partial pressure of the gas applied to the solvent. At some point, an equilibrium will be reached where the amount of gas exiting the solvent will equal the amount that enters the solvent. This point is called "*equilibrium"*. At a constant temperature, this point will depend on the solubility of the gas in the solvent. If the gas has a high affinity for the solvent, more solvent will enter the gas before some will start to exit and vice-versa. This equilibration point can be illustrated mathematically by measuring the concentration of a gas or volatile present on top of a solvent and compare it to the concentration of the gas *dissolved in the solvent* once they have reached equilibrium. Let us consider the following experiment: We have two containers of equal volume (1 L). One contains isoflurane at 10% and the other blood at 37^{o}C. (see *figure 8*).

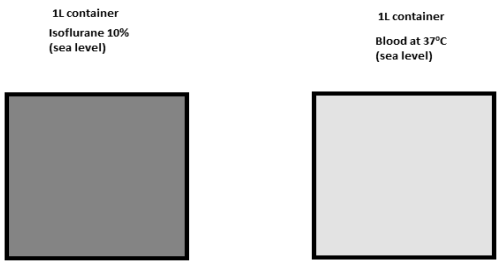

Figure 8 - Two containers of equal volume

We now connect the two containers and allow equilibration to take place. (*see figure 9*).

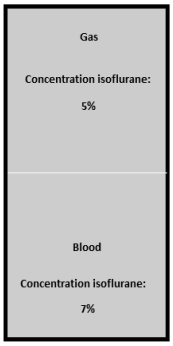

Figure 9 - Two containers at equilibrium

This will allow some of the isoflurane to dissolve in the blood and reach equilibrium. We now measure the new isoflurane concentrations in both the blood and gas and find 5% present as gas and 7% present in blood. Since we kept the volumes and temperature constant, we can determine the ratio of vapour to solvent for isoflurane:

$$Ratio = \frac{Concentration_{blood}}{Concentration_{gas}} = \frac{7\%}{5\%} = 1.4\ (dimensionless\ number)$$

This ratio can be used to determine the affinity of the gas for a specific solvent and is called the *blood-gas partition coefficient* (represented with the symbol *lamda*: $\boldsymbol{\lambda_{blood\text{-}gas}}$), since it is dimensionless (the units of concentration has cancelled out). In the above example, it implies that every millilitre of blood will contain 1.4 times more isoflurane than that present per millilitre in the gas phase. The higher the $\boldsymbol{\lambda_{blood\text{-}gas,}}$ the greater the amount needed to saturate the blood, therefore the more will be absorbed by the blood before the volatile will exit the blood in the gaseous phase. Therefore, IA with low $\lambda_{blood\text{-}gas}$ rapidly saturate blood, and rapidly create a partial pressure *on top of blood.* And vice-versa.

We can measure the partial pressure of gases in equilibrium with blood, at the end of expiration, hence the name: *end-tidal partial pressure*, or *end-tidal concentration*. The measured partial pressure of anaesthetic agent at end of expiration is therefore similar to alveolar partial pressure (P_{alv}). This partial pressure is the partial pressure at equilibrium with ***pulmonary venous blood.*** Pulmonary venous blood is returned to the left atrium where it eventually gets pumped as ***arterial blood*** to the rest of the body. In other words, *alvoelar gas* is in equilibrium with pulmonary venous blood, which is almost exactly equal to arterial blood. Arterial blood is then distributed to different organs and tissues. These tissues will then be exposed to the same partial pressure measured in the alveolar gas, since this is the amount of gas ***that could escape the blood after it was in equilibrium***. It will be this partial pressure that will ***drive the pressure gradient across the blood, into the tissues*** (one of which is ***the brain***). Measuring the *alveolar anaesthetic partial pressure* (or concentration in most gas analysers) will therefore indicate the partial pressure ***that the brain is exposed to***. This is of great significance to the anaesthesiologist.

Factors that determine the rate of rise of the alveolar partial pressure of anaesthetic gas/vapour

In order to achieve the desired pharmacodynamic effect, the effect-site of the IA needs to reach a specific concentration or partial pressure. We have already discovered that *end-tidal partial pressure or concentration* is similar to that partial pressure of which the brain will be exposed to (which is usually the effect-site of most IA). We will now discuss the factors that will determine the rate of rise (and later the rate of dissipatioin) of this partial pressure. Mathematical expressions exist to describe each of the mechanisms mentioned below. They become exeedingly complex and have been omitted from the text. The reader is referred to reference [4], chapter 26, page 645-650

Solubility

The solubility of agents are represented in *table 2*. The definition of $\boldsymbol{\lambda_{blood\text{-}gas}}$ is discussed above. The greater the $\boldsymbol{\lambda_{blood\text{-}gas}}$**,** the greater the amount of anaesthetic dissolved in the blood and the greater the

absorption of agent by the blood. If we compare different agents with different $\lambda_{blood\text{-}gas}$, we can see how agents with low $\lambda_{blood\text{-}gas}$ will have a rapid rise in $P_{alveolar}$. The reason for this is that more soluble agents will have a greater amount taken up by the blood and therefore ***take longer to saturate the blood*** before being able ***to escape the blood*** and ***produce a partial pressure on top of the blood***. If we keep everything constant except the solubility of the agent, we can demonstrate the different rate of rise of $P_{alveolar}$ with a graph. *Figure 10* illustrates this with the commonly used anaesthetic gases and vapours. It compares the inhaled partial pressure (being kept constant) to the alveolar partial pressure over time.

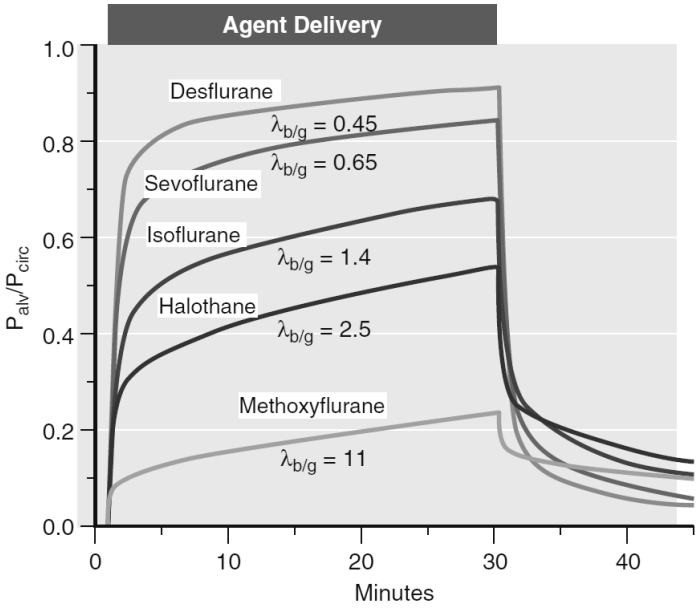

Figure 10 - Solubilities and rate of P_{alv} rise
Adapted from Miller RD, Cohen NH, Eriksson LI, et al. Miller's Anesthesia. 8th ed. Philadelphia: Elsevier Saunders; 2015.

The least soluble IA have a rapid rise in $P_{alveolar}$ while the more soluble agents have a slow rise. Another deduction we can make from the above figure, is that the amount of *uptake* of anaesthetic will be a graph that looks inverse to that of $P_{alveolar}$. (see *figure 11*) Initially, uptake will be high.

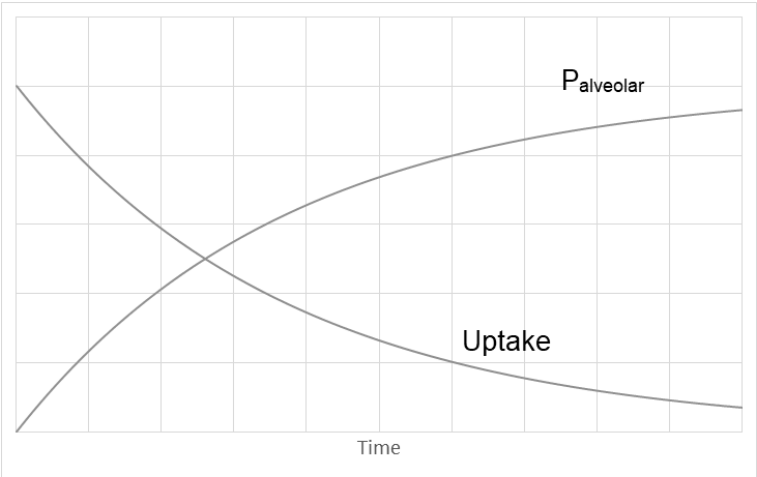

Figure 11 - $P_{alveolar}$ vs Uptake over time

When there is true equilibrium between all the tissues, blood and alveolar gas, then no more uptake will take place and $P_{alveolar}$ will be constant (this never occurs under clinical conditions). Insoluble IA will have a rapid fall in uptake over time. Again, this illustrates that the insoluble IA will rapidly saturate blood and therefore rapidly *decrease uptake*, while simultaneously rapidly *increasing the alveolar partial pressure*.

Cardiac Output

The effect of cardiac output (CO) can sometimes be confusing. We assume that a fast moving circulation can rapidly get anaesthetic agent to the brain and therefore rapidly induce anaesthesia. This would be true if we had no limit to the amount of anaesthetic agent we could deliver to the circuit and pulmonary system and that the pulmonary system had a limitless ability to absorb delivered agents. In truth, we see that an increase in cardiac output will (as we have assumed) rapidly redistribute the anaesthetic agents to the brain, ***but also to the rest of the tissues***. This results in a drop in the anaesthetic content in the blood and therefore a ***decreased alveolar partial*** pressure. A ***fast cardiac output*** will therefore ***slow the rise in alveolar partial pressure*** and therefore slow the induction of anaesthesia. This can be seen during induction of anaesthesia of paediatric patients that are distressed and crying (with high CO and therefore slow induction) versus the calm relaxed patient (with normal CO and faster induction). Similar effects are seen with intravenous agents. This effect is also ***exagerated for the more soluble agents*** (*see figure 12*). The more soluble the agent, the higher the uptake. With high CO *even more* will be taken up resulting in further reducing $P_{alveolar}$. *Figure 12* illustates the effect of varying cardiac output on desflurane and halothane alveolar partial pressure. Even though the rise in alveolar partial pressure is slower in desflurane during high CO, this effect is much more profound with halothane (being almost 6 times more soluble in blood than desflurane).

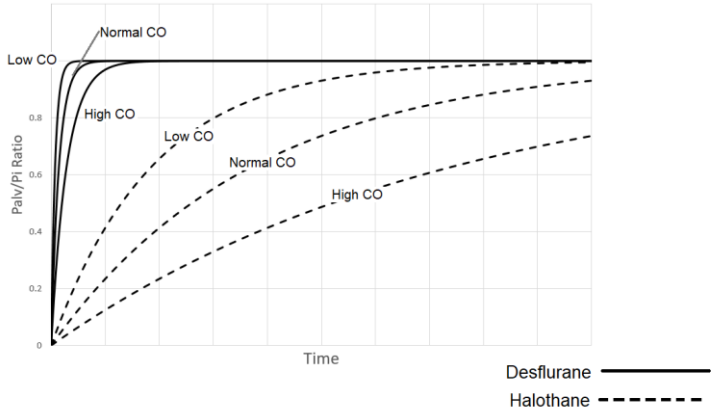

Figure 12 - The effect of CO and solubility on rate of rise of $P_{alveolar}$

Ventilation

Minute volume affects rate of uptake. Increasing *MV* will result in the opposite effect of increasing CO. With increasing *MV*, the amount of anaesthetic being delivered to the pulmonary airspace is increased, and therefore increasing the rate of rise of $P_{alveolar}$. The impact of solubility is similar to that of CO variation: the more soluble agents will have greater benefit on increased *MV.* Since only alveolar ventilation contributes to agent absorption, the amount of dead-space ventilation will also influence rate of uptake. Increasing the ***dead-space ventilation*** will decrease anaesthetic uptake and therefore slow rise of $P_{alveolar}$. Note that once dead-space ventilation increases, we can no longer accept that *end-tidal partial pressure is equal to* $P_{alveolar}$. During high dead-space ventilation, the *end-tidal* measurement will likely rise rapidly, but since this is more a reflection on the partial pressure of the dead-space volume, we should not assume similar alveolar partial pressures. This effect is exagerated in agents with a low $\lambda_{blood\text{-}gas}$: with high dead-space ventilation, alveolar ventilation is reduced, and since the agent has a low $\lambda_{blood\text{-}gas}$, the little alveolar ventilation that *does* take place will absorb very little agent.

Pulmonary shunting (*right to left shunting*) will shunt blood across without any anaesthetic agent uptake in the shunted blood. It can result from pathological processes (lobar collapse, consolidation, etc.) or iatrogenically from selective lung- or lobar ventilation. *Figure 13* demonstrates an ongoing anaesthetic with significant pulmonary shunt and a theoretical scenario where ***pulmonary arterial blood*** (Q_{pulm}) has a partial pressure of 0.8 kP_a isoflurane – remember, pulmonary arterial blood comes from the right ventricle and is usually deoxygenated blood. After gas exchange the ***pulmonary venous blood*** now has a partial pressure of 1.2 kP_a isoflurane (just as an example). This will now mix with the shunt fraction (Q_{shunt}) with 0.8 kP_a isoflurane (similar to Q_{pulm}). Depending on the size of the shunt fraction, the ***systemic arterial partial*** pressure will now admix to ***a lower partial pressure***.

The larger the shunt fraction, the lower the arterial partial pressure and the greater the impact on alveolar partial pressure rise rate.

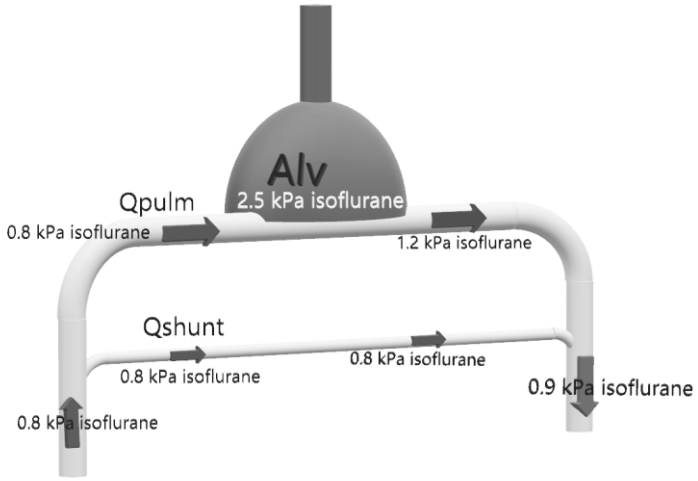

Figure 13 - Model of pulmonary shunting

And as with increased dead-space ventilation, *end-tidal* measurements become unreliable: from *figure 13* we can deduce that the pulmonary venous partial pressure is 1.2 kP_a, and therefore the measured *alveolar partial pressure (end-tidal)* will also be 1.2 kP_a. However, the arterial partial pressure (P_{art}) admixes down to 0.9 kP_a and therefore the partial pressure that the brain will be exposed to will be 0.9 kP_a. We therefore see a discrepancy between P_{art} versus $P_{alveolar}$. As with increased dead-space ventilation, pulmonary shunting has its greatest impact on agents with low $\lambda_{blood\text{-}gas}$. *Figure 14* demonstrates the different effect of pulmonary shunting on N_2O (relatively insoluble) and halothane (relatively more soluble). N_2O suffers more from the effect. The broken lines indicate how $P_{arterial}$ and $P_{alveolar}$ change during significant pulmonary shunting. With the more insoluble N_2O, the discrepancy between $P_{arterial}$ and $P_{alveolar}$ is greatest. During shunting (right to left), the $P_{arterial}$ is always lower than $P_{alveolar}$.

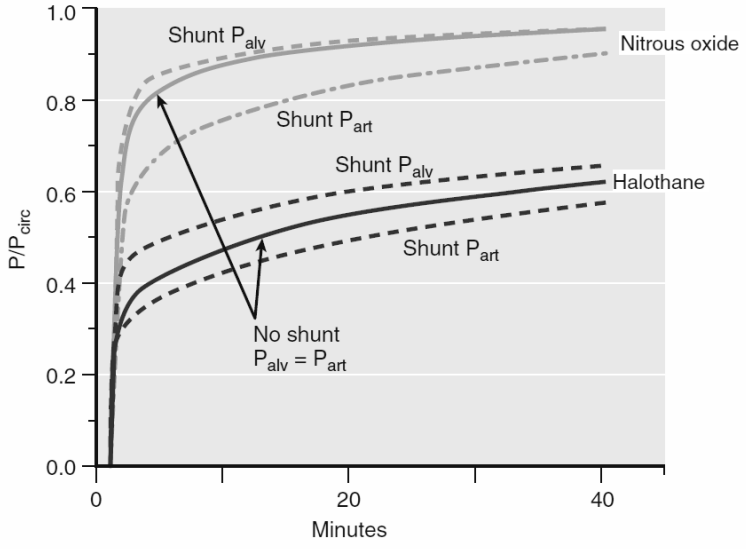

Figure 14 - N_2O versus halothane during pulmonary shunt

Clinically, this can affect the induction of anaesthesia in patients with pathological shunts, such as those with congenital cardiac disease. ***Right to left shunting will delay the induction of anaesthesia***. During ***left to right shunting***, some of the pulmonary venous blood is shunted back to the pulmonary arterial system, increasing the partial pressure of anaesthetic agent. With moderate left to right shunting, there is a small but discernible accelerated induction of anaesthesia, with the effect significantly smaller than that seen with right to left shunting.[15] See *figure 15*.

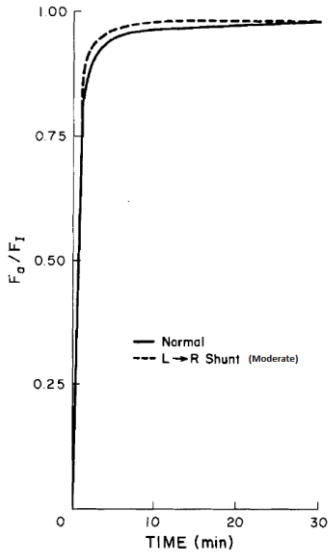

Figure 15 - Moderate Left to Right shunting
Adapted from Tanner GE, Angers DG, Barash PG, et al. Effect of left-to-right, mixed left-to-right, and right-to-left shunts on inhalational anesthetic induction in children: a computer model. Anesth Analg 1985;64(2):101–7.

A large left tot right shunt might have a greater effect, but with a large left to right shunt, systemic perfusion is decreased and as a result anaesthetic uptake is reduced. This has a variable effect on the rate of rise of the alveolar partial pressure of anaesthetic agent: initially slowed and then faster. (*see figure 16*). ***We can deduce that left to right shunting in isolation has little effect on induction or emergence of anaesthesia***.[15]

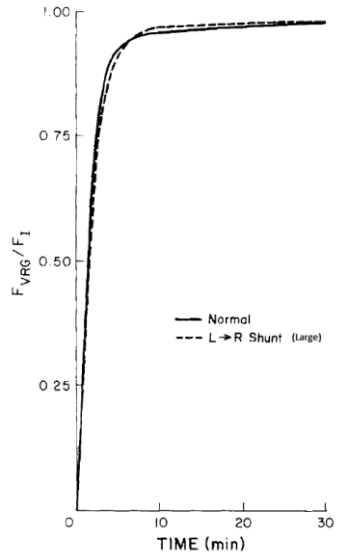

Figure 16 - Large Left to Right shunting
Adapted from Tanner GE, Angers DG, Barash PG, et al. Effect of left-to-right, mixed left-to-right, and right-to-left shunts on inhalational anesthetic induction in children: a computer model. Anesth Analg 1985;64(2):101–7.

Uptake of anaesthetic by various tissues

Up to now we have discussed the complexities of anaesthetic uptake from the lung by the pulmonary venous blood. We have seen how various manipulations of the CO, *MV* and solubility of agents can change the rate of uptake and subsequently the rate of rise of $P_{alveolar}$. We also briefly touched on the effects of tissue absorption during high or low CO. We will now focus more on the uptake and distribution of anaesthetic agents to the tissues.

As with blood, each tissue has a specific solubility partition coefficient for a given gas or volatile.

Complex studies have evaluated these for individual tissues. In *table 2* the blood-brain partition coefficient is given. We can see that it ranges between 1 and 2 with some exceptions. Thus, blood and brain have very similar affinities for currently used inhaled anaesthetic agents. If we compare that to other tissues such as muscle or fat, the affinity for IA increases with fat having more than a 10 fold increase in affinity. Since these tissues are perfused to a lesser degree, their uptake is therefore perfusion limited. To simplify this model, we can separate organs and tissues into different groups in terms of their perfusion. Vessel-rich organs (brain, heart, liver, kidney and endocrine organs) account for 10% of the bodyweight, but receive 75% of the cardiac output. This large perfusion permits the vessel-rich group to receive and remove the largest portion of anaesthetic agent. This group has blood-tissue partition coefficients in the range of 1 to 2, therefore having similar affinity for the IA when compared to blood. This group will therefore equilibrate most rapidly with the inhaled anaesthetic partial pressure. In fact, this group is so well perfused that it takes less than 10 minutes to reach equilibrium, if the inspired partial pressure is maintained. For the rest of the organs and tissues that are less well perfused (muscle, fat, etc.), IA will be taken up continiously, with the fat compartment never reaching total equilibrium under clinical conditions. This will result in an initial large discrepancy between inhaled anaesthetic partial pressure and alveolar partial pressure that decreases over time, but never truly becomes zero. A useful way to represent equilibrium of different tissues, is to compare the partial pressure in the tissue with the inspired partial pressure ($\frac{P_{tissue}}{P_{inspired}}$). *Figure 17* illustrates how different tissue compartments will absorb and equilibrate to the inspired partial pressure over time during a 60 minute anaesthetic exposure.

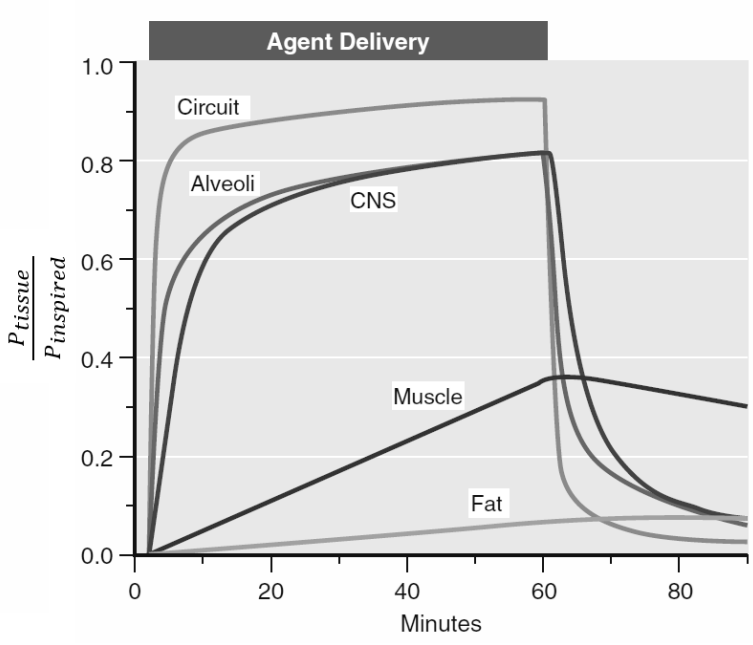

Figure 17 - Tissue:Inspired partial pressure ratio over time at constant inspired partial pressure Adapted from Miller RD, Cohen NH, Eriksson LI, et al. Miller's Anesthesia. 8th ed. Philadelphia: Elsevier Saunders; 2015, page 649.

In obese patients, both the fat mass and lean body mass increases. Here we can display one of the clinical applications of the above theory. To maintain an alveolar partial pressure above $MAPP_{50}$, the obese patient will require more administration of IA as he/she will absorb more in the tissues. The effect of obesity on wash-in kinetics is very little,[16] however, its effect on *context-sensitive* emergence times are quite significant. Studies from obese patients consistently indicate a prolonged emergence from equipotent anaesthetic partial pressures, and a more rapid recovery from the use of less soluble agents such as desflurane.[17] Another patient group that has altered wash-in kinetics, is children. With their relatively high CO ***and MV*** (on a per kilogram basis) and their ***increased perfusion of the vessel-rich tissues***, they tend to accelerate their rate of rise of $P_{alveolar}$ (this difference being more profound for the more soluble IA). Therefore, they have a more rapid induction of anaesthesia. (see *figure 18*)

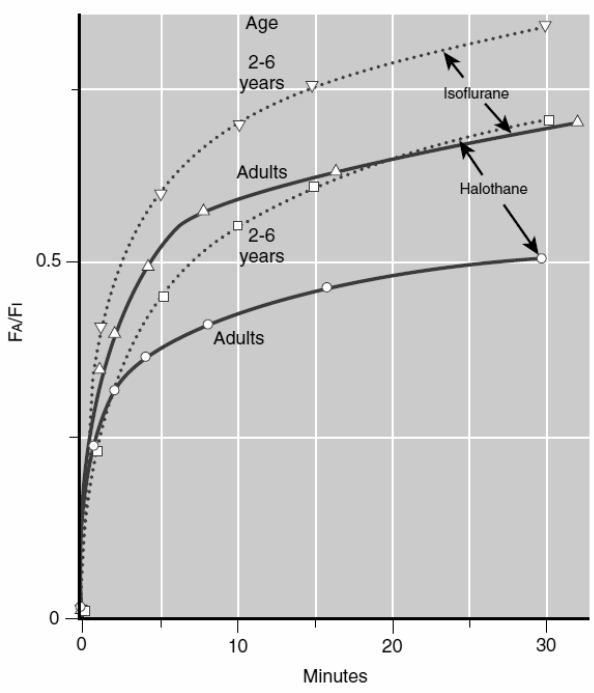

Figure 18 - Wash-in kinetics in adults vs children
Adapted from Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP. Miller's Anesthesia. 7th ed. Churchill Livingstone; 2009

Unfortunately, this rapid wash-in accounts for the large amount of IA taken up by the different tissues and explains the large accumulation of IA in the other compartments. For this reason, their wash-out times are prolonged.

In summary:
The rate of rise of alveolar partial pressure is important to the anaesthetist, since it is indicative of the partial pressure of IA that the brain is exposed to. For an IA to enter the brain, it must be absorbed in the pulmonary venous blood and then transported to the brain. The IA can only exit the blood once the blood has absorbed sufficiently high amounts as to reach an equilibrium with the gas phase in the lungs. This relationship of amount in the blood versus amount able to escape the blood is referred to as the *blood-gas partition coefficient* and reflects the IA solubility in blood. High $\boldsymbol{\lambda_{blood\text{-}gas}}$ results in high blood absorption and therefore slow rise in alveolar partial pressure. Therefore, slow induction, but also slow emergence.

Increased ***cardiac output*** increases the rate of absorption *but also* the rate of redistribution to tissues and therefore slows the rate of rise of alveolar partial pressure of IA. Thus, high CO causes slowed induction. ***Increased ventilation*** will expedite the rate of rise of alveolar partial pressure since it expedites wash-in kinetics of the IA. This can be used to counteract increases of cardiac output.

The ***solubility of tissues*** will also determine their effect on the rate of rise of alveolar partial pressure. Tissues with high perfusion will rapidly equilibrate and accounts for the bulk of anaesthetic uptake and therefore rate of rise of alveolar partial pressure. Slowly perfused tissues and tissues with very high solubility will continue to take up anaesthetic and is responsible for the remaining $P_{inspired}$:$P_{alveolar}$ difference. The different effects can be further illustrated by comparing different patient groups.

Recovery from anaesthesia – Context sensitive nature

The routes of clearance of IA are similar to the routes of administration. Additionally, similar principles will govern the rate of clearance:

Circuit wash-out is governed by similar principles as wash-in (as discussed earlier). High FGFs and absent IA will rapidly clear the anaesthetic circuit and prevent rebreathing from occurring in the circle system. Smaller circuits will also wash out quicker.

Increased MV will increase clearance. This will unfortunately also lower the partial pressure of CO_2

with potential detrimental effects (cerebral vasoconstriction, decreased cerebral blood flow). Slowing of *MV* can reduce clearance, an occurrence sometimes seen during spontaneous ventilation, since *MV* is decreased by IA. An increased *CO* will slow emergence since more gas-exchange volumes will be required to accommodate the larger pulmonary blood flow. In other words, unless the *MV* is also increased, high *CO* will delay wash-out of IA. *The solubility* of IA has a significant impact on wash-out. Highly soluble IA will slow wash-out, since their uptake during agent delivery was higher, because of their higher affinity for blood and tissues. Agents with low solubility will rapidly wash-out and clear.

An important factor with regards to emergence, is the ***context-sensitive nature of the preceding administration.*** To understand this, let us first determine what is meant by *context-sensitive.* If we consider the definition of a *context-sensitive half-time**, it is the time taken for a 50% reduction in amount of a specific agent in a specific compartment after administration to that compartment has ceased***. To apply this to intravenous pharmacokinetics, we can define the *context-sensitive half-time* of propofol by stating that it is the time taken to half the propofol plasma concentration after administration has ceased. Therefore, if we apply the definition to inhalational agents, it would state that an inhalational agent's *context-sensitive half-time* is the time taken to decrease to 50% of the previous *alveolar partial pressure (end-tidal partial pressure)* after administration has ceased. The *context* refers to the duration of administration, or the cumulative administered dose. After a prolonged case, the cumulative dose administered will be higher, therefore more IA will be absorbed by tissues, which will prolong time to emergence.

To achieve a partial pressure in the brain below emergence threshold, IA need to be cleared not only from the blood, but also the other tissues. As the circuit is washed out, the lungs will follow. Since no more IA is added to the blood, the blood will start to clear. This now generates an IA pressure gradient from the tissues *towards* the blood. The tissues will now start to release their IA back to the blood and in so doing, keep the blood partial pressure from falling. Only once the tissues have significantly decreased their content, will the blood and brain partial pressure fall. The amount of tissue wash-out to occur before emergence will set in, is determined by the amount that was absorbed by the tissues. This will depend on the solubility of the IA in the tissues, but also on the duration of exposure, since most tissues will not be completely saturated at the end of most anaesthetic exposures. IA with low $\lambda_{blood\text{-}gas}$ will be less affected by the preceding context of administration. In other words, agents with low $\lambda_{blood\text{-}gas}$ will not display the same prolongation in wash-out after prolonged exposure. Some of the historic IA had high rates of metabolism, which had significant impact on their clearance. The modern IA have little or no metabolism and therefore metabolism has negligible effect on wash-out times. Even halothane's metabolism does not appear to significantly alter its wash-out kinetics, since it has such a high solubility in tissues.[18]

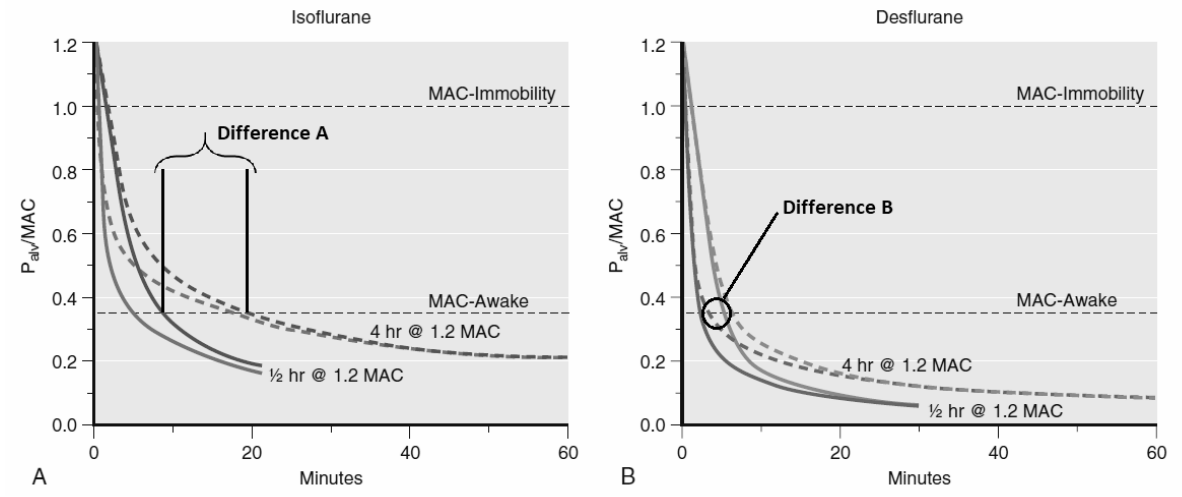

Figure 199 - Difference in time to MAC-awake
Adapted from Miller RD, Cohen NH, Eriksson LI, et al. Miller's Anesthesia. 8th ed. Philadelphia: Elsevier Saunders; 2015.

Figure 19 shows two differences: in *figure 19.A*, the solid lines indicate the wash-out curves of isoflurane (with $\lambda_{blood\text{-}gas}$ = 1.4) after a 30 minute anaesthetic at 1.2 x MAC, with the dashed lines indicating wash-out after a longer (4 hour) anaesthetic at similar concentration exposure (1.2 x MAC). *Difference A* is the time difference between the two isoflurane emergence points, where the curves

cross the MAC-awake threshold. This difference is approximately 10 minutes. In *figure 19.B* this exact same comparison is done with desflurane (with $\lambda_{\text{blood-gas}}$ = 0.42). *Difference B* is less than 3 minutes and therefore almost negligible in clinical practice. We can deduce two facts from the above graphic: the preceding context to which an anaesthetic is administered, will determine its elimination or wash-out (this applies to all agents, inhalational or intravenous); the more insoluble agents are by far less affected by the preceding context of administration when compared to their more soluble counterparts. The clinical relevance of this is clear: for prolonged cases, an agent with lower solubility will be more rapidly washed out. For short procedures, this effect is less profound.

To wash-out 50% of the initial partial pressure is considered a good predictor of *context-sensitive* emergence times. However, a 50% drop in isoflurane from 1.2kP_a to 0.6 kP_a is still above $MAPP_{awake}$. Therefore, 80% and 90% wash-out times have been considered more clinically relevant, while 99% and even 99.9% wash-out times might indicate *complete* recovery from anaesthesia.[18,19] At the extremes of wash-out times (>80%) the complexities of tissue solubility and perfusion are much more evident. Isoflurane, sevoflurane and desflurane have 50% wash-out times of less than 5 minutes regardless of duration of anaesthetic – see *figure 20.*

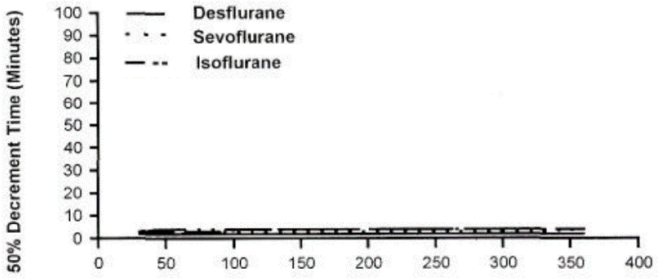

Figure 200 - 50% wash-out times for volatiles[19]

When we compare the ***80% wash-out times*** for the different volatiles, the difference is remarkable. See *figure 21.*

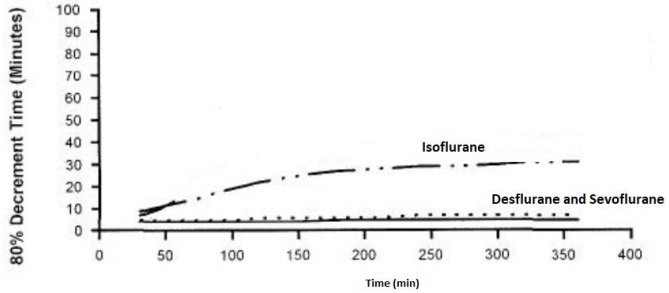

Figure 21 - 80% wash-out times compared[19]

The 80% wash-out or decrement time for isoflurane appears to increase more over time and reaches a plateau at approximately 30 minutes after about 2 hours of administration at 1x$MAPP_{50}$. If we compare the 90% decrement times of the different inhalational anaesthetics, this is further exaggerated by agents with increased solubility – *see figure 22.*

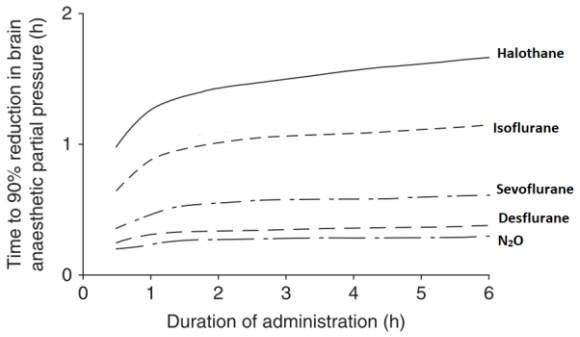

Figure 22 - 90% wash-out decrement times of the different inhalational anaesthetics[18]

While 90% wash-out might seem irrelevant to obtain $MAPP_{awake}$, consider the effects of concomitant administration of other agents that can synergistically reduce both $MAPP_{50}$ and $MAPP_{awake}$ (potent synthetic opioids, benzodiazepines, etc). Additionally, certain pathological conditions can necessitate a decrease to below $MAPP_{awake}$ before safe return of protective airway reflexes, such as premature neonates or patients with obstructive sleep apnoea syndrome, with increased sensitivity to the inhalational agents.

The concentration effect (that results in the augmented inflow and concentrating effect) and the second gas effect has not been included in this text – the reader is referred to any of these references.[4,9,20]

In summary:
Recovery from anaesthesia begins when the circuit is washed out by increasing FGF that is devoid of anaesthetic agents (in other words contain only oxygen and air). The same principles that govern rate of rise of alveolar partial pressure of IA will govern the rate of wash-out. Increased *CO*, decreased *MV* and highly soluble IAs will prolong the wash-out time. Similar effects can be considered for pulmonary shunting (right to left shunting will delay wash-out). An important aspect to consider is the *context-sensitive nature* of the preceding administration of anaesthesia (in other words, the duration and dose preceding wash-out). Longer administration times will result in prolonged wash-out times, again more significant in the IA with increased solubility in blood and tissues. Different *decrement times* exist for specific agents and for different decrement thresholds (50% vs 80% vs 90% wash-out time). Agents with low solubility will have less influenced decrement times as opposed to more soluble agents. Metabolism has a negligible role in wash-out kinetics of IA.
Some useful calculators and documents can be downloaded from this Dropbox folder:

or tinyurl.com/2018-22

At a glance: Summaries according to sections:

Circuit kinetics
The anaesthetic circuit has its own wash-in kinetics. The wash-in kinetics are dependent on:
a) FGF (higher FGF, smaller τ_{circ}, quicker wash-in)
b) Circuit volume (lower volume, smaller τ_{circ}, quicker wash-in)
c) P_{del}, the amount of anaesthetic in the fresh gas flow, which can also be the *vaporiser setting* (higher setting, more inhaled anaesthetic delivered, greater *pressure gradient* $(P_{del} - P_{circ})$ to circuit, quicker wash-in)

For rapid wash-in to occur, a large FGF and/or a small circuit volume should be selected. Changing the vaporiser output can further alter the rate of obtaining a specific target amount and therefore also contribute to altering the wash-in kinetics. Each combination of circuit volume and FGF give a unique

circuit wash-in time constant called tau (τ) which can be used to predict when wash-in or wash-out will occur. Circuit wash-in or wash-out half-time can be calculated as $\tau \times 0.693$. To calculate near total wash-in or wash-out (98%): $\tau \times 4$. Similar physical laws govern wash-out of the circuit, with the notable exception that one can only decrease to vaporiser output to zero and not give a *negative* number of vapour to further expedite wash-out, whereas one can give significantly high wash-in pressures with most modern vaporisers.

Pulmonary airspace kinetics
Once a patient is connected, the patient's lung compartment adds additional complexity to the kinetics, but with similar dependable variables:
a) Minute volume (higher *MV*, smaller τ_{pulm}, quicker wash-in)
b) Lung volume (lower volume, smaller τ_{pulm}, quicker wash-in)
c) Higher inhaled partial pressure from circuit, higher *pressure gradient into* $(P_{circ} - P_{pulm})$ lungs, quicker wash-in.

Uptake by blood and tissues and the alveolar partial pressure of IA
The rate of rise of alveolar partial pressure is important to the anaesthetist, since it is indicative of the partial pressure of IA that the brain is exposed to. For an IA to enter the brain, it must be absorbed in the pulmonary venous blood and then transported to the brain. The IA can only exit the blood once the blood has absorbed sufficiently high amounts as to reach equilibrium with the gas phase in the lungs. This relationship of amount in the blood versus amount able to escape the blood is referred to as the *blood-gas partition coefficient* and reflects the IA solubility in blood.

High $\boldsymbol{\lambda_{blood\text{-}gas}}$ results in high blood absorption and therefore slow rise in alveolar partial pressure. Therefore, slow induction, but also slow emergence.

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Recovery from anaesthesia begins when the circuit is washed out with by increasing FGF that is devoid of anaesthetic agents (in other words contain only oxygen and air). The same principles that govern rate of rise of alveolar partial pressure of IA will govern the rate of wash-out. Increased *CO*, decreased *MV* and highly soluble IAs will prolong the wash-out time. Similar effects can be considered for pulmonary shunting (right to left shunting will delay wash-out). An important aspect to consider is the *context-sensitive nature* of the preceding administration of anaesthesia (in other words, the duration and dose preceding wash-out). Longer administration times will result in prolonged wash-out times, again more significant in the IA with increased solubility in blood and tissues. Different *decrement times* exist for specific agents and for different decrement thresholds (50% vs 80% vs 90% wash-out time). Agents with low solubility will have less influenced decrement times as opposed to more soluble agents. Metabolism has a negligible role in wash-out kinetics of IA.

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The Inflammatory Cascade
The physiology of the systemic inflammatory response syndrome (SIRS)

Dr Howard Radford

Private Practice
Lecturer- Dept of Anaesthesia
University of the Witwatersrand

Disclaimer
These notes have not been peer reviewed. Please refer to appropriate text books and journal articles.

Definitions

In 1991 the American College of Chest Physicians/ Society of Critical Care Medicine consensus conference defined the Systemic Inflammatory Response Syndrome (SIRS) and sepsis.

> **SIRS**: systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following: temperature > 38 ^{o}C or < 36 ^{o}C; heart rate >90 beats/min; respiratory rate > 20 breaths/min; and white blood cell count > 12000 mm-3, < 4000 mm-3 or > 10% immature (band) forms
>
> **Sepsis**: Systemic response to infection, manifested by two or more of the following as a result of infection: temperature > 38 ^{o}C or < 36 ^{o}C; heart rate > 90 beats/min; respiratory rate >20 breaths/min; and white blood cell count > 12000 mm-3, < 4000mm-3 or > 10% immature (band) forms

Given that sepsis is similar to SIRS except for a causative factor much is common to the physiology of both syndromes. In this handout I will explore the physiology that gives rise to the symptoms and signs described above.

Physiology

Over the last 20 years a profound understanding of the physiology of cellular biology and its interrelationships and the predisposition to develop SIRS, sepsis, severe sepsis, and septic shock has evolved.

This complex condition is becoming more clearly defined. The process consists of the interaction of chemical mediators and cells and involves the expenditure of energy and damage and destruction of host tissue. It is now clear that after the first pro-inflammatory mediators are released, the body mounts a compensatory anti-inflammatory reaction to regulate the inflammatory process. When the balance between these two groups is lost many of these substances become harmful and the cellular components are further activated.

This syndrome initially involves the innate immune system which responds rapidly to the exposure of “foreign material” and activates the adaptive system. The adaptive system which is made up of lymphocytes serves to enhance the innate immune system. It takes days to reach maximum effect. The innate immune system is not enhanced by exposure and does not discriminate between foreign substances. This system is mediated by, macrophages, monocytes, natural killer cells and polymorphonuclear cells (neutrophil).The receptors involved are able to recognized highly conserved elements of cellular structures and are thus able to respond to a wide diversity of stimuli (LPS, Peptidoglycans, manams, flagellin, heat shock proteins, DNA, RNA, Hyaluronan, Phospholipids, ß-defensin). This strategy is termed pattern recognition and the receptors that elucidate the effect are termed as pattern recognition receptors. Figure 1 shows a simplified flow diagram of the development of the inflammatory response.

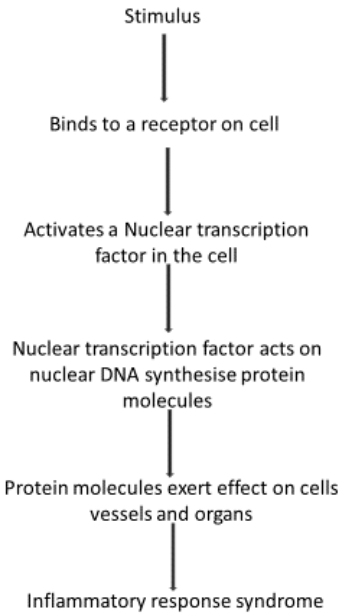


Figure 1
Flow diagram of the development of the inflammatory response

The cells

Mononcytes, macrophages and dendritic cells

Circulating monocytes can, either migrate to the site of inflammation, and differentiate to dendritic cells and function as antigen-presenting cells or colonize different organs as tissue macrophages - Kuppfer cells in the liver, alveolar macrophages and peritoneal macrophages. Monocytes and macrophages are the most effective producers of pro and anti-inflammatory mediators. At times they may produce more anti-inflammatory mediators than proinflammatory mediators. Macrophages and monocytes are thus cellular key components in both initiating and regulating the innate immune response. They may rapidly produce large amounts of inflammatory mediators in addition to phagocytosis and clearance of micro-organisms. Macrophages sense danger through their wide range of innate immune receptors like CD14, Toll like receptors (TLR), complement and Fc-receptors.

Polymorphonuclear neutrophils (Neutrophils)

Their capacity of phagocytosis exceeds that of macrophages, but their capacity of synthesizing RNA and proteins is low. Neutrophils possess numerous granules and vesicles rich in anti-microbial proteins released in phagosomes to kill micro-organisms, and enzymes used for degradation of cellular structures during migration from the vessels to the inflamed site. They are also rich in membrane receptors utilized in phagocytosis and trafficking. At the site of infection, neutrophils recognize PAMP on the surface of micro-organisms through their Pattern recognition receptors (PPRs) including CD14 and TLR. Neutrophils also utilize their surface Fc- and complement-receptors to bind the microorganisms opsonized by antibodies and complement components.

Phagocytosis involves many mechanisms and enzymes leading to the elimination of pathogens in the phagosomes. This occurs either by:

- oxygen dependent mechanisms via production of reactive oxidants (ROS) [O_2^- (superoxide), H_2O_2 (hydrogen peroxide), HOCl (hypochlorous acid), OH^- (hydroxyl radical), NO_2Cl (nitryl chloride), $ONOO^-$ (peroxynitrite), RNHCl (chloramines) and MPO_3+O_2) (compound III)]. The main source of ROS in neutrophils is the membrane bound enzyme complex nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Inflammatory mediators, immune complexes, and bacteria attached to membrane receptors activate NADPH oxidase and the respiratory burst.

- oxygen independent mechanisms via involvement of proteolytic enzymes and anti-microbial peptides from granules and vesicles and acidification of the endosomes containing micro-organisms.

Neutrophils may present degraded pathogen peptides to T cells and play a role in linking innate and adaptive immunity. Neutrophils are constitutively apoptotic. In critical illness Neutrophil survival is prolonged and apotosis is delayed. This is mediated by many factors- pro-inflammatory cytokines, TLR, components of micro-organisms and their transendothelial migration. Nuclear transcription factors (NF-jB) activates transcription of genes promoting survival as well as genes that inhibit apoptosis. Notably, phagocytosis of bacteria activates neutrophils.

Endothelium

Endothelium is a modulator of systemic inflammation. Endothelium participates in the synthesis of inflammatory mediators and is a target for some of the released mediators.

Lymphocytes

B- and T-lymphocytes mediate adaptive immunity. T-lymphocytes constitute the primary link between innate and adaptive immune responses. Antigen presenting cells, such as monocytes/ macrophages, dendritic cells and B cells present processed antigens to T cell with either major histocompatibility (MHC) class II or MHC class I. Upon the presentation of antigens with MHC class II and in the presence of appropriate co-stimulatory signals, T cells produce a variety of cytokines like IL-2, INF-c and IL-10. The secretion of these cytokines drives T-cell differentiation, initiation of anti-microbial activity in mononuclear cells and antibody production by B cells. T Helper Cells 1 produces INF-c and IL-2 and enhance cellular inflammation, and T Helper Cells 2 produce IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13 and enhance humoral activation. T Cell $_{reg}$ produce transforming growth factor-b and IL-10 and have a negative regulatory role in the immune response. CD8+ cytolytic T Cells can identify and kill cells which are infected with intracellular pathogens.

Natural killer cells

Natural killer (NK) cells are an important source of inflammatory cytokines. They recognize danger signals but depend on signals from dendritic cells, monocytes, and macrophages, to be activated and respond to danger signals elicited by pathogens. NK cells can also differentiate between damaged own cells and healthy cells.

Mast cells

Although they have a primary role in anaphylaxis they have also been shown to produce inflammatory cytokines. The exact role in inflammation is still to be elucidated.

Pattern recognition receptors (PPRs)

These can be classified into 2 groups: transmembrane and cytosolic

Transmembranes PPRs

Toll – like Receptors (TLR)

The best characterized of these receptors is the toll like receptors (TLRs) These receptors are very similar to the Interleukin – 1 Receptor (IL – 1R) and the Toll receptor found in Drosophila (the fruit fly) [Hence the name]. They are Type 1 transmembrane polypeptide receptors. The N terminal is found extracellularly. The extracellular domain contains many leucine rich repeats. There is a single transmembrane domain. The C terminal of the chain is found intracellularly and links to a cascade via a protein Myd -88 that results in the activation of Nuclear Transcription Factor (NF – κB) and IFN-regulatory factor transcription factor.

Ten human TLRs have been identified five are found in the cell membrane TLR 1,2 4,5,6 and four TLR 3, 7, 8, 9 are found in the lysosomal membrane.

Each respond to a different biological component. Several microbial molecules bind or activate them: - Lipopolyssacharide (LPS) [TLR 4], Lipoteichoic Acid [TLR 2], Peptidoglycans [TLR 2], Manams [TLR

2], Hyaluronanan [TLR 2], Double stranded RNA [TLR 3], Single stranded RNA [TLR 7&8], DNA [TLR 9]. An extracellular adapter protein e.g. MD-2 binds to the TLR and confers responsiveness to these components. A carrier protein HMGB 1 carries DNA and RNA across the cell membrane into the cytosol so that they can bind to their TLRs found on the lysosome.

Cytosolic PPRs

NOD – like - receptors

These receptors are more varied in structure than TLRs but are very similar to Nod 1 and Nod 2 proteins and structure they are thus known as Nod like Receptors (NLR). They consist of 3 parts: A ligand recognition site which has a large number of leucine rich moieties (similar to TLRs); A nucleotide zone which mediates dimerisation and a signaling module which dictates the final outcome of NLR activation - activate transcription factors NLR 1 or activation of inflammasome (multi protein complex consisting of capsase, a protease that converts pro IL – 1 to IL-1) or NLR 2.
These receptors are activated by uric acid, toxins and flagellins that have reached the cytosol. Activation of inflammasome may also cause cell death which lacks the features characteristic of apoptosis.

TLRs and NLRs interact to enhance inflammation. Both activates transcription factors and thus amplify the production of cytokines etc. TLR signaling produces ProIL- 1 as well as components of the inflammasome, which in turn cause the conversion of ProIL-1 to IL-1

RIG -1-like receptors

The first of these receptors to be identified was retinoic acid inducible gene 1 – RIG. These receptors detect foreign RNA and DNA. Foreign DNA is sensed by DNA dependent activator IFN regulatory factor (DAI). Both these PPRs will result in activation of genes producing IFNs. As yet, there is no evidence of links with TLRs or NLRs

Nuclear transcription factors (NF)

There are numerous nuclear transcription factors which are responsible for the transcription of the genes responsible for the proteins that mediate the effects of inflammation. The best described is NF – κB.

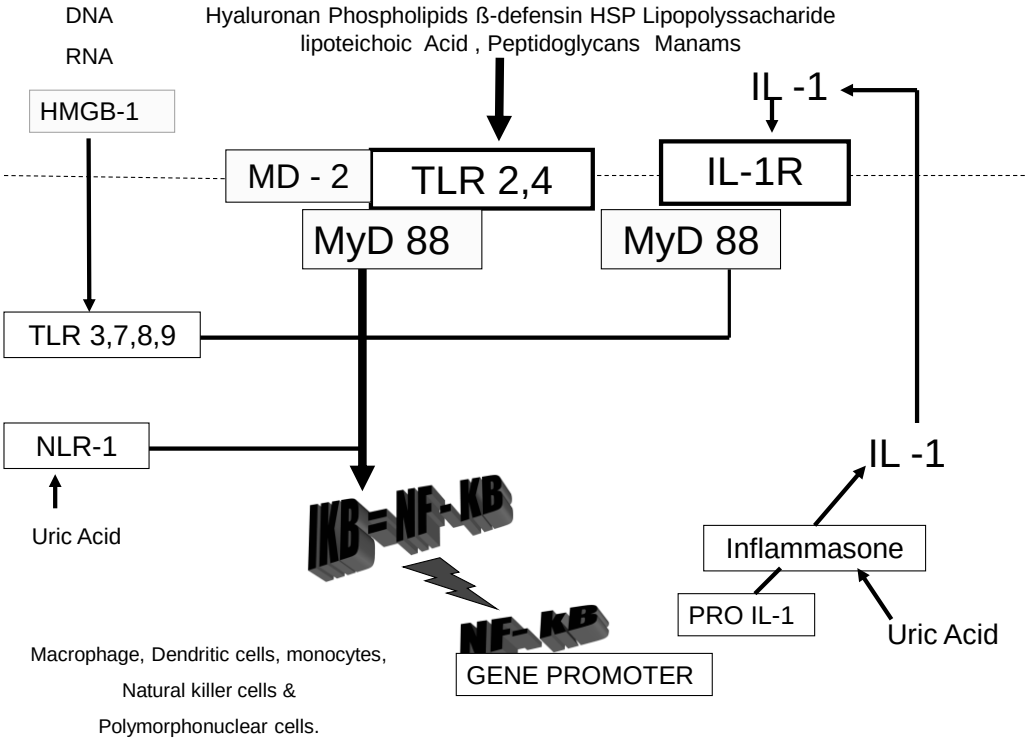
NF – κB

In the unstimulated cell, NF – κB is found in the cytoplasm bound to proteins IκBα and IκBβ which prevents it entering the nuclease. When the TLR is stimulated it activates a cascade of kinases similar to interleukin 1 (IL –1) (see below) which causes phosphorylation of the complex and frees NF– κB which enters the nuclease. Oxidants, viruses, IL-1 and Tumor Necrosis Factor (TNF) can also release NF– κB from the complex directly. In acute lung injury and acute respiratory distress syndrome, IL-1, TNF and LPS, activate NF– κB in the alveolar macrophage. In the nuclease NF– κB binds to the promoter site of the genes which produces:

- pro-inflammatory cytokines (IL-1, TNFα);
- chemotactic cytokines (IL-8);
- adhesion molecules and immune receptors;
- inducible Nitric Oxide Synthetase (iNOS);
- Cyclooxygenase;
- Granulocyte Macrophage Colony Stimulating Factor(GM SCSF)
- Platelet Activating Factor (PAF).

The process is terminated by the transcription of the gene that results in the synthesis of IκBα which then binds up NF– κB.

NF– κB effects are inhibited by glucocorticoids, which increase the transcription of IκBα and aspirin in high concentration. IL-10 inhibits by increasing IκKβ. Ghotoxin found in aspergillus is a potent inhibitor. Vitamin C & E and n-Acetyl cystein are weak inhibitors.



Gene products related to inflammation

Cytokines

Cytokines are small (less than 80kDa) glycosylated, proteins, produced by all nucleated cells. UV light, hyperosmolarity and presence and adherence of foreign materials stimulates the release of these cytokines. Proinflammatory cytokines, TNFα, IL-1 and IL-8 are the most important mediators promoting SIRS and sepsis.

Tissue Necrosis Factor is a produced as a prohormone of 233 amino acids, which is processed to a 157-amino acid mature protein. There are two distinct forms Alpha and Beta, which bind to the same receptor and produce similar but not identical effects.
LPS enhances TNF α gene transcription as does Interferon – γ. TNFα synthesis is inhibited by glucocorticoids, IL-4 and IL-6.

TNFα is central to the development SIRS sepsis, severe sepsis and septic shock. Besides activating NF– κB, it also activates Phospholipase A_2 (PL A_2), Cyclooxygenase (COX), iNOS, adhesion molecules and chemokines directly. This results in the formation of arachnodonic acid, PgE_2 and prostacycline and leukotrienes, Nitric oxide (NO) and the increase in platelet activating factor (PAF) and neutrophils migration. Centrally TNFα induces sleep, fever and anorexia. TNFα inhibits lipid uptake in adipose tissue and enhances lipogenesis in the liver. TNFα causes efflux of amino acids from skeletal muscle and decreases proteolysis in the liver. TNFα stimulates the anterior pituitary, adrenal cortex and pancreas and causes activation of the sympathetic nervous system. TNFα has also been shown to cause myocardial dysfunction and direct damage to the endothelium.

Interleukin 1 (IL – 1) exist in two forms Alpha and Beta. The synthesis and the release of Il-1 is initiated by microorganisms, toxins, NF– κB, TNFα and itself. Gene transcription results in the formation of Pro IL-1. Activation of the inflammasome via NLR 2 results in cleavage of the Pro IL-1 to give rise to IL-1 which is secreted by the cell. IL - 1 binds to a specific receptor Interleukin 1 Receptor (IL – 1R) that couples with an accessory protein. The intracellular portion forms an active complex with an adapter protein (MyD88) and 2 putative serine threonine kinase (IRAK & IRAK2). A protein (TRAF6) bridges it to another protein kinase which ultimately activates NF– κB.

IL – 8 is a potent chemokine that facilitate movement of leukocytes from the vascular to the interstitial compartment. It also induces degranulation of the leukocytes. It has also been shown to have antigenic activity. TNFα and IL-1 stimulate its secretion.

Nitric Oxide Synthetase and Nitric Oxide

Nitric Oxide Synthetase (NOS) is found in many cells. Two types are distinguished namely constitutive and inducible forms.

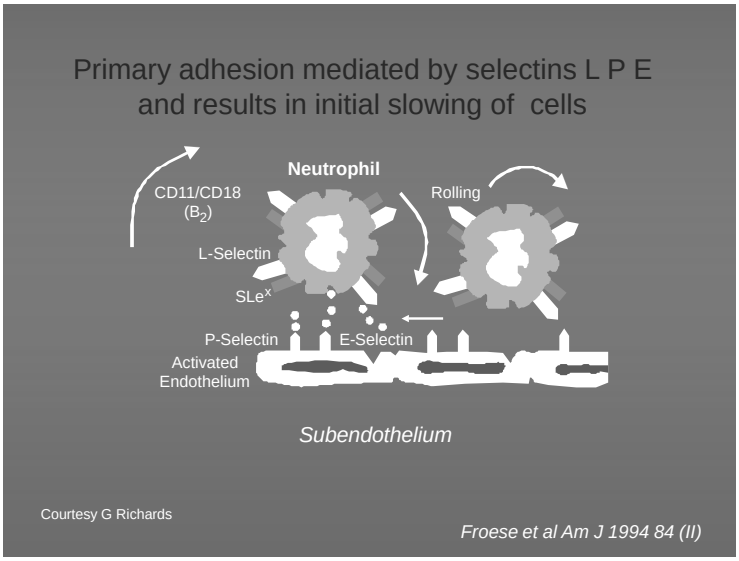
There are two isoforms of *constitutive NOS*. eNOS and nNOS found in the endothelium and the neurons respectively. This form is calcium dependent. The synthesis of NO by this enzyme has an important role in vasodilatation, inhibition of platelet function and neurotransmission.
The *inducible NOS* is not normally active. Small amounts are found in the lung, small intestine and platelets. It does not require calcium for its action. In SIRS and sepsis, NF– κB, TNFα, IL –1 and bacterial toxins cause its induction. IL-4, IL-10 and glucocorticoids suppress the induction of iNOS activity.

NOS catalyses the conversion of l- arginine and O_2 to l – citrulline and NO. NO is the smallest known biologically active molecule. It is an uncharged molecule thus it can diffuse easily across the cell membrane. NO has an unpaired electron in its outer shell thus it is a free radical and is highly reactive having a half life of 2 – 30 seconds. In the target cells it complexes with iron containing proteins such as haeme and nucleic acids. NO causes smooth muscle relaxation by activating cGMP, myocardial depression, and platelet inactivation. It also damages nuclear protein, oxidizes phospholipids, interacts with super oxides and inhibits mitochondrial respiration.

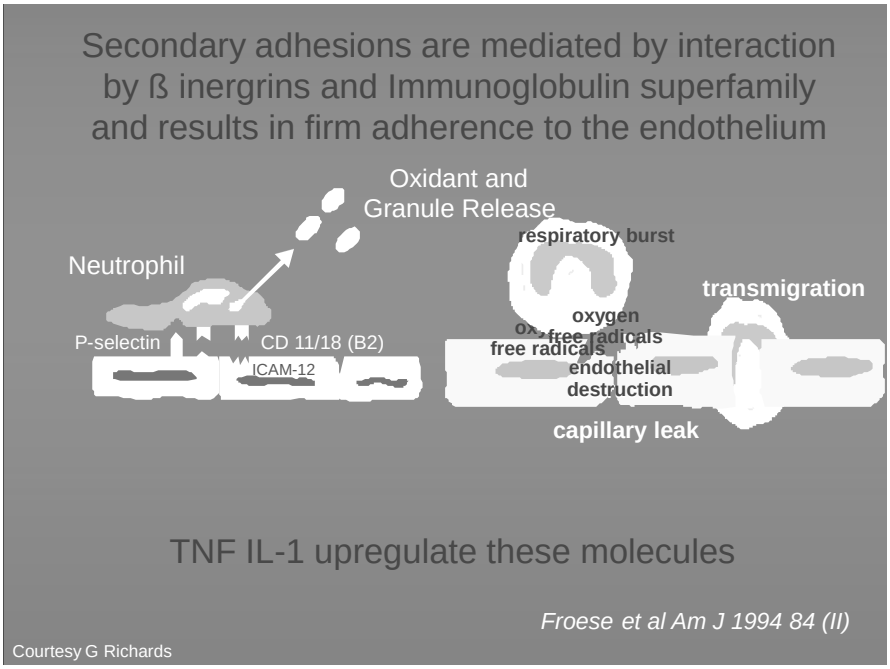
Adhesion Molecules

Neutrophils are the prime cause of organ damage in SIRS and sepsis. The process whereby the Neutrophils mediate organ damage requires several steps, involving the adhesion of the neutrophil to the vascular endothelium. Adhesion requires initially a mechanical slowing of the flowing cells and primary bonding of the cell to the endothelium and secondarily stabilization of the bonds and in some cases, changes in shape of the cell. Leukocytes travel slowly through the microcirculation. If the perfusion pressure drops or the neutrophils become activated, they will adhere to the vessel wall. Primary adhesion is mediated by *Selectins* – L, E and P. L Selectin is found on the leukocytes and mediates a low affinity-rolling interaction with the E Selectin found on the endothelium. The latter is synthesized and expressed under the influence of cytokines. P Selectin is found in platelets and the endothelium.

Secondary adhesion is mediated by interaction of *β-intergrins* found on the neutrophil and *Immunoglobulin superfamily* found in the endothelium. This needs conformational changes before optimal binding occurs. This process results in firm adherence of the neutrophil to the endothelium.



There are 2 forms of integrins - β1 and β2. β1- integrin VLA- 4 is found in lymphocytes and monocytes and binds to the endothelial immunoglobulin superfamily and VCAM-1 is expressed in response to cytokines. β2-intergrins are found in the neutrophil and monocytes. Mac – 1 and LFA - 1 is the β2 intergrins found on PMNLs. Chemokines promote the movement of Mac-1 from the intracellular milieu to the surface membrane. These intergrins bind to the ICAM immunoglobulin super family found on the endothelium. ICAM-2 is found constitutively on the endothelium. Inflammatory cytokines increase the production of ICAM-1. ICAM-1 recognize LFA-1. ELAM-1 and GMP-140 are Immunoglobulin super family upregulated by IL –1 and TNF and bind to the neutrophil intergrins in SIRS and sepsis. Intergrins and the immunoglobulin super family also aid in the diapedesis through the endothelium. Endotoxin, PAF, IL - 8, TNFα, Granulocyte Colony Stimulating Factor, shear stress and exposure to collagen found in the basement membrane results in priming of the neutrophil. A second stimulus is needed to cause degranulation and the release of elastases, peroxidases, arachnodonic acid, gelatinase and collegenase



Some of the foreign material engulfed by the macrophages monocytes and NK cells may be extruded onto the cell surface so becoming antigen presenting cells (APC). Peptide fragments derived from extracellular protein following phagocytosis are expressed on the surface bound to class II Major Histocompatibility Complex (MHC) and are recognized by T Helper cells (Th). In contrast peptides derived from protein synthesis in the cells from foreign genetic material are presented with class I MHC molecules and are recognized by cytolytic T cells. This process is enhanced by TNFα. The Th. cells when activated produce cytokines, which enhance the development and differentiation of the Th. cell. Th. 1 cells are produced by, the action of Interferon, IL – 2 and IL – 12, and activate cell mediated immunity. Interferon-γ is produced by the lymphocytes in response to IL - 1. Th.2 cells are produced by the effects of IL-4, IL – 6, IL- 10, IL-13 and control B cell development and thus mediate humoral responses. B cells have membrane bound antibodies. Antigens bind to the antibodies activating the cell to produce and secrete antibodies

Activation of the classic and alternate compliment cascade occurs during sepsis. This may be directly as a result of direct interaction with the organism or foreign toxins, or as a consequence of cytokine activity. IL - 2 and IL - 6 induce the synthesis of C-reactive proteins (CRP) in the liver. CRP binds to phosphocholine on the cell membrane and induces the compliment cascade. Products of the compliment cascade C3a and C5a can also enhance the release of TNF, IL-1 and IL-6. Together these factors may have a synergistic effect on the on the activation of granulocyte.

Anti-inflammatory mediators

At the same time as the inflammatory mediators are released, Anti-inflammatory mediators are elucidated. These are cytokines (IL – 4, IL-10, IL-11, IL-13), cytokines inhibitors (Tissue growth factor

B blocks the effects of IL-1, TNF and LPS) or soluble cytokines receptors (IL –1rc inhibits binding to receptor of IL-1, soluble TNF receptors).These factors work to diminish macrophage and monocytes expressing antigen linked to MHC and reduce the effects of inflammatory mediators. It is possible that the compensatory process can be inappropriate resulting in immunosuppression giving rise to a Compensatory Anti-inflammatory Response Syndrome (CARS).

Conclusion

Although much is now known about the physiology of systemic inflammation there is still much that needs to be explained. Recent advances in biotechnology and the sequencing of the human genome has lead to an increase in the understanding of SIRS Sepsis Severe Sepsis and Septic Shock. None of these problems is likely to be determined by a single gene action but rather by the simultaneous activity of a multitude of genes. Many sets of genes are involved in determining a particular response. Functional genomics will provide the scientific basis for the improvement in accuracy of diagnosis and prognosis and the identification of new therapeutic interventions.

References

Available on request

Suggested article

Castellheim A. et al. Innate Immune Responses to Danger Signals in Systemic Inflammatory Response Syndrome and Sepsis Scandinavian Journal of Immunology 2009 69, 479–491

The Endothelial Glycocalyx

Dr Christella Alphonsus

Dept of Anaesthesia & Perioperative Medicine
University of Cape Town

Overview

The glycocalyx is a complex gel layer that coats all healthy vascular endothelium. This layer exists in dynamic interaction between flowing blood and the endothelial cell wall. It plays a pivotal role in vascular protection, modulation and haemostasis.

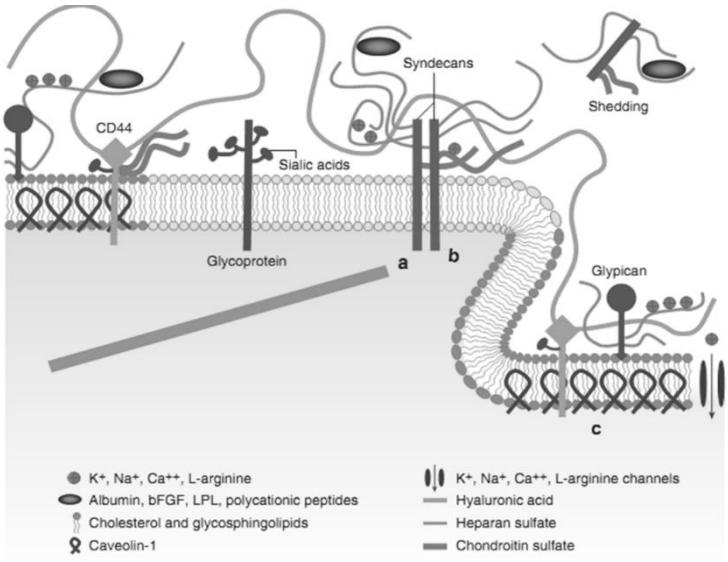
Components

The endothelial glycocalyx is essentially made up of glycoproteins or proteoglycans but there is great diversity in structure and function within these two groups.

Proteoglycans have a protein core to which are attached negatively charged glycosaminoglycan (GAG) side chains. There are different types of proteoglycans and they vary according to: the core protein size, the number of GAG side chains and whether they are bound or not bound to the cell membrane. Syndecans and glypicans are first bound to the cell membrane and the GAG side chains are attached later. Other proteoglycans (perlecans, versicans, decorins, biglycans, mimecans) are first bound to GAGs and then secreted by the endothelial cells.

There are five types of GAG side chains: heparan sulphate makes up 50–90%, with the remainder composed of hyaluronic acid and chondroiton, dermatan and keratin sulphates. Hyaluronic acid is the only GAG not usually bound to a core protein and forms viscous solutions with water.

Glycoproteins act as adhesion molecules and contribute to the coagulation, fibrinolytic and haemostatic systems. These include E and P selectin which are expressed after stimulation by histamine, thrombin, interleukin-1 and tumour necrosis factora (TNF-α). Ligands for leucocyte and platelet adhesion ICAM-1, ICAM-2, VCAM-1, PECAM-1 are also expressed within the glycocalyx.



Weinbaum S, Tarbell JM, Damiano ER: Annu. Rev. Biomed. Eng. 2007

Structure

The glycocalyx provides a luminal mesh for the binding of proteins and other active molecules. The composition and dimensions of the glycocalyx fluctuate as it continuously replaces material sheared off by flowing plasma. The thickness of the glycocalyx thickness varies throughout the vasculature, between 0.1 and 1 µm.

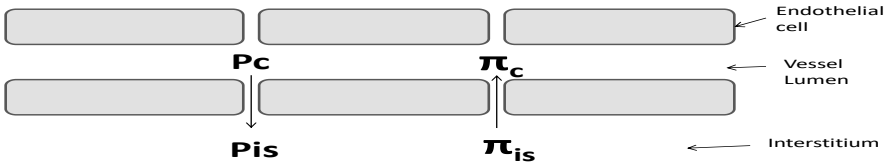
The glycocalyx has a net negative charge that is dependent on GAG side chain sulphation which is modified by physiological and pathophysiological stimuli. This affects protein binding and vascular permeability. The charged mesh of the glycocalyx acts as a macromolecular sieve, repelling negatively charged molecules, as well as white and red blood cells and platelets. Macromolecules larger than 70 kDa are excluded from the glycocalyx. Albumin is 67 kDa and thus leaks through the glycocalyx despite its mostly negative charge. However it does also carry positive charge, and this amphoteric nature helps it to also bind to the glycocalyx. This binding reduces the hydraulic conductivity across the vascular barrier.

The binding of plasma constituents to the inert framework of glycocalyx produces the physiologically active endothelial surface layer (ESL). The ESL regulates vascular permeability, influences blood cell-vessel wall interactions, affects rheology and controls the microenvironment.

Physiology

Models of fluid movement across the vascular barrier, traditionally based on the principles derived by Starling in 1896, have been modified by our understanding of the endothelial surface layer.

Starling, who was not aware of the existence of the glycocalyx, described four forces that regulate fluid homoeostasis. The sum of tissue oncotic and luminal hydrostatic pressures forces fluid out of the vessel into the tissue. The sum of tissue hydrostatic and luminal oncotic pressures forces fluid out of the tissue into the vessel. According to this model there is a great movement of fluid both out of and into vessels. However, experiments over the past 25 years do not show this great fluid movement.



$$F/A = C_H [(P_c – P_{is}) – \sigma (\pi_c - \pi_{is})]$$

Figure1: The Starling principle (Jv/A = volume filtered per unit area, Lp = hydraulic conductance, Pc = capillary hydrostatic pressure, Pis = interstitial hydrostatic pressure, σ = osmotic reflection co-efficient, πc = capillary oncotic pressure, πis = interstitial oncotic pressure

To resolve this problem, three key components of Starling's equation were revised.

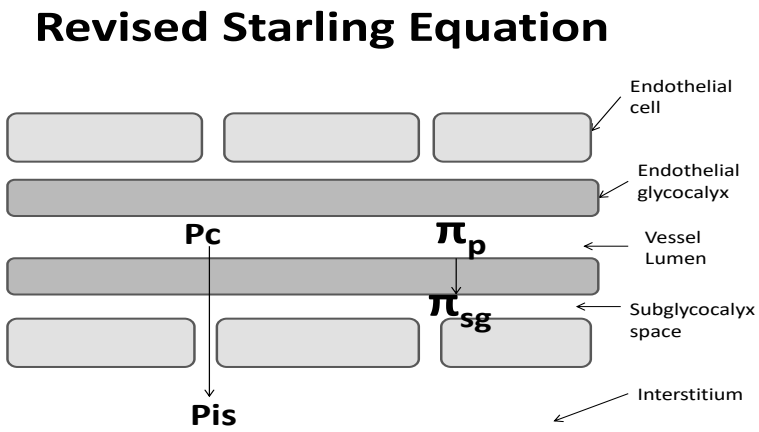
1) Sustained venous reabsorption does not occur in most tissues, only in specialized tissues like the kidney and intestines. This was shown by Levick in 1996. In contrast the net force between venular hydrostatic pressure and tissue hydrostatic and oncotic pressures favours venous filtration.
The alternate route for fluid to return to the circulation is the lymphatic system. However, measurements of lymphatic flow showed it was too slow to clear fluid produced by the capillary filtration rate according to Starling's model.

2) Capillary filtration rate is much less than Starling predicted. This is a logical conclusion since a scenario of no venous reabsorption, low lymphatic flow and high capillary filtration should lead to tissue oedema, but it doesn't.

Why is the capillary filtration rate it less than Starling predicted? And how is this possible?

3) The endothelial surface layer reduces hydraulic conductivity. Adamson et al. showed that oncotic forces are only set up across the endothelial surface layer on the luminal aspect of the endothelial cell, not across the whole capillary wall. Capillary filtration rate is tightly regulated. The oncotic pressure differences across the endothelial surface layer reach equilibrium very quickly, thereby leading to less fluid filtration.

The glycocalyx model presents an efficient system that resolves all three of these problems. Fluid filtration is regulated at the point at which it begins – within the capillary lumen by the endothelial surface layer



$$F/A = C_H [(P_c – P_{is}) – \sigma (\pi_p – \pi_{sg})]$$

Figure 2: Revised Starling principle Jv/A = volume filtered per unit area, Lp = hydraulic conductance, Pc = capillary hydrostatic pressure, Pis = interstitial hydrostatic pressure, σ = osmotic reflection co-efficient, πp = oncotic pressure on plasma-side of ESL, πis = oncotic pressure in subglycocalyx space

Pathology

There are certain pathological processes that affect glycocalyx integrity and leads to shedding and disruption of constituents.

This list broadly includes:

1) Ischaemia/reperfusion
2) Sepsis
3) Volume loading
4) Hyperglycaemia
5) Atherosclerosis
6) Trauma/cardiac and aortic bypass surgery

Effects of shedding:

- capillary leak
- oedema
- accelerated inflammation
- platelet aggregation
- hypercoagulability
- loss of vascular responsiveness

Assessment of the glycocalyx

The glycocalyx is a difficult structure to visualize because it is destroyed by conventional dyeing and fixation techniques. Dynamic assessment of the glycocalyx is also difficult and current technologies are not readily available and can only assess the glycocalyx in easily assessible parts of the circulation, eg. sublingual microcirculation. These novel technologies are: Orthogonal polarization spectral imaging (OPS) and side-stream dark field imaging (SDF).

Therapies

These therapies may provide benefit due to their effects on the glycocalyx:

-Avoiding hyperglycaemia
-Albumin
-Steroids in septic shock
-Sevoflurane
-Avoiding hypervolaemia
-Statins

Therapies such as TNFα inhibition, antithrombin III and infusions of glycocalyx constituents are still experimental.

References

1. Available on request: email: csalphonsus@gmail.com

SBA SESSIONS

Note that the questions posed in each SBA session have been grouped such that most will relate to the series of three lectures which follow that session. In the interests of covering more domains of the Part One syllabus within the confines of this course, a few of the questions in each session are unrelated to the lecture programme.

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SBA SESSION ONE:
Siggaard Anderson vs Stewart, Blood gas interpretation, Electrodes

Question 1

Regarding electrodes:

a. Reduction occurs at the anode
b. Oxidation results in the loss of electrons
c. The only parameters directly measured in the blood gas analyser are the partial pressure of pCO2 and blood pH
d. A fuel cell (also known as Galvanic sensor) requires an external current to drive the cathode reaction

Question 2

Regarding electrodes:

a. Carbon dioxide concentration can be measured by a Clark electrode
b. Clark electrodes use noble metals such as gold and lead as the cathode.
c. In line or mainstream carbon dioxide monitoring is by a Severinghaus electrode.
d. A glass electrode can measure hydrogen ion concentration.

Question 3

Regarding exercise physiology:

A 30-year-old woman is training for her second Ironman. She decides to add high intensity intervals to a 3-hour long training session. During these bursts of high intensity intervals, the physiological changes are characterized by:

a. Fall in pH due to increased lactic acid generation.
b. Increase in blood flow to muscle of 500-1000 ml per 100 g muscle per min.
c. Increase in oxygen consumption up to 20 times above resting oxygen consumption.
d. Increased ventilatory drive due to changes in arterial concentrations of oxygen and carbon dioxide.

Question 4

A 3 year old child with an unrepaired ventricular septal defect (VSD) is anaesthetised for an incision and drainage of a submandibular abscess. Intravenous access and face mask ventilation are difficult. Five minutes into the procedure the child begins to desaturate. There is no evidence of airway obstruction, air entry is equal bilaterally, but the oxygenation does not improve on FiO_2 1.0. What is the most likely cause of the arterial hypoxaemia?

a. Right to left intra-cardiac shunt
b. Increased oxygen consumption
c. Ventilation-perfusion inequalities
d. Left to right intra-cardiac shunt

Question 5

In the healthy lung of an adult in the upright position:

a. The V/Q inequality results in a greater arterial O2 content of blood at the top than at the bottom of the lung
b. Ventilation (V) at the top of the lung (per g tissue) is greater than at the bottom
c. Blood flow (Q) to the top of the lung (per g tissue) is much greater than at the bottom
d. Ventilation/perfusion ratio is lower at the top of the lung than the bottom

Question 6

A previously well 22 year old female presents to the emergency room with acute dyspnoea and chest pain. On examination she has a swollen left calf, her oxygen saturation is 88% and the calculated A-a O2 gradient is 27 mmHg. What is the most likely cause of the arterial hypoxaemia?

a. Ventilation-perfusion mismatching
b. Alveolar hypoventilation
c. Right to left arterial shunt
d. Diffusion disequilibrium

Question 7

A normal plasma hydrogen ion concentration equivalent to a pH of 7.4 is:

a. 40 mmol/L
b. 40 pmol/L
c. 40×10^{-7} mol/L
d. 40×10^{-7} nmol/L

Question 8

Regarding pK_a:

a. the higher the pKa the stronger the acid
b. depends on the concentration of the molecule in solution
c. is a constant and hence has no effect on the pH of a solution
d. is the pH at which protonated and deprotonated concentrations of the molecule are equal

Question 9

A 30-year-old male participates in a 400 m sprint competition against his fellow work colleagues. The predominant source of ATP generation comes from:

a. ATP stores within the muscle cells
b. Glycogen
c. Lactate
d. Phosphocreatine

Question 10

A 30-year-old healthy man runs for 2 hours with a heart rate average of 130 bpm. From previous exercise testing he knows this heart rate equates to a respiratory exchange rate (RER) of 0.80. The predominant source of ATP generation comes from?

a. Aerobic glycolysis
b. Anaerobic glycolysis
c. Fatty acid oxidation
d. Proteins

Question 11

A homozygous atypical $E_1^a E_1^a$ variant:

a. Has a dibucaine number > 20
b. Has an incidence of 1:3200
c. Has a block duration of 1 hour
d. Has an incidence of 1:100000

Question 12

With regard to malignant hyperpyrexia:

a. The syndrome is caused by a defect in the ryanodine receptor RYR1
b. The maximum dose of Dantrolene is 10 mg/kg
c. The *in vitro* contracture test is the gold standard for the diagnosis of MH
d. The initial dose of Dantrolene is 1 mg/kg

Question 13

You are the anaesthetist on call in ICU. One of your patients has severe Gram negative sepsis with septic shock. The microbiology report shows a carbapenem resistant organism. Which method of resistance is the organism most likely employing?

a. Altered metabolic pathways
b. Drug inactivation by enzymes in the peri-plasmic space
c. Efflux pumps
d. Target-site alteration

Question 14

Regarding Aminoglycosides, which statement is true?

a. They rely on time-dependant microbial killing
b. The best way to achieve a large area below the concentration-time curve is to administer smaller, more frequent doses
c. The maximum dose that may be used clinically is limited by the toxic effects to the host
d. Smaller, frequent doses help minimise toxicity by maintaining low, sustained concentrations of drug.

Question 15

Which group of antibiotics exert their effect through inhibition of bacterial cell wall synthesis by incorporating itself into the bacterial cell wall?

a. Aminoglycosides
b. Beta-lactams
c. Macrolides
d. Quinolones

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Answers

Question 1

Correct answer

b. Oxidation results in the loss of electrons

Marking memorandum

reduction occurs at the cathode (RED CAT)
OIL RIG oxidation = loss of electrons Reduction = gain of electrons
pO2 is also directly measured
A fuel cell is able to supply its own current

Question 2

Correct answer

d. A glass electrode can measure hydrogen ion concentration.

Marking memorandum

CO_2 measured by Severinghaus electrode
Lead is not a noble metal
A Severinghaus electrode cannot measure respiratory CO_2: CO_2 must be in solution

Question 3

Correct answer

c. Increase in oxygen consumption up to 20 times above resting oxygen consumption.

Marking memorandum

The pH remains nearly normal even during high intensity training due to the buffer capacity of $HCO3^-$.
Blood flow to muscles at rest is usually 2-4 ml/100 g muscle/min. During maximal exercise this increases to about 100 ml/100 g muscle/min.
How respiration is stimulated during exercise is not completely understood. It is thought to be a combination of motor centre activity, afferent signalling from proprioceptors in muscles and joints as well as alterations in the sensitivity of chemoreceptors to PO_2 and PCO_2. The changes in PaO_2 and $PaCO_2$ are insufficient to account for the large increase in respiration.

Question 4

Correct answer

a. Right to left intra-cardiac shunt

Marking memorandum

This is an example of reversal of an intra-cardiac left-to-right shunt to a right-to-left shunt through the VSD. This is due to an increase in pulmonary vascular resistance (hypercapnia & acidosis secondary to difficult face mask ventilation) combined with a reduction in systemic vascular resistance (vasodilating effects of anaesthetic agents). In a ventilation-perfusion mismatch primarily due to shunt the arterial hypoxaemia will not be corrected by an increase in inspired oxygen concentration.

Increased oxygen consumption - under general anaesthesia, the normal response is a *reduction* in oxygen consumption

Ventilation-perfusion inequalities - as explained, the arterial hypoxaemia is due primarily to *shunt*, and is a more accurate description than ventilation-perfusion mismatch, which also includes dead space

Left to right intra-cardiac shunt – a left to right intra-cardiac shunt through a VSD would result in *increased* pulmonary blood flow and would not cause cyanosis

Question 5

Correct answer

a. The V/Q inequality results in a greater arterial O2 content of blood at the top than at the bottom of the lung

Marking memorandum

The higher V/Q at the top of the lung has this effect.
Ventilation is greater at the bottom of the lung. The opposite is true for the last two statements (c. & d.)

Question 6

Correct answer

a. Ventilation-perfusion mismatching

Marking memorandum

In the context of the history of acute dyspnoea, chest pain and swollen calf in the setting of an INCREASED A-a O_2 gradient, the most likely diagnosis is a pulmonary embolus resulting in a V/Q mismatch causing an INCREASED A-a O_2 gradient. Differential diagnosis would include pneumonia and further investigations would be required to confirm the diagnosis.

In hypoventilation it would be expected that the alveolar and arterial PO2 would both be reduced and the A-a O_2 gradient would be NORMAL

Right-to-left arterial shunts can cause a significant increase in the A-a O_2 gradient. However, there is no previous clinical history to suggest a pre-existing left to right shunt (e.g. tetralogy of fallot) and this history is suggestive of an acute event.

Diffusion equilibrium may contribute to an increased A-a O_2 gradient, but is rare and highly unlikely in this case

Question 7

Correct answer

c. 40 x 10^{-7} mol/L

Marking memorandum

The normal pH of 7.4 corresponds to a $[H^+]$ of 40nmol/L. This is the same as 40x10^{-7} mol/L

Question 8

Correct answer

d. is the pH at which protonated and deprotonated concentrations of the molecule are equal

Marking memorandum

The lower the pKa the stronger the acid. pKa like pH is expressed as a negative logarithmic function.

$$pK_a = -\log_{10}[K_a]$$

The strength of an acid relates to the ability of a substance to donate protons(H^+)

pKa is a constant for a substance and is uneffected by the concentration of the molecule in solution. It effectively tells us how a substance will react under different pH values. If a substance has a pKa of 8 (eg local anaesthetics) and is placed in plasma it will accept $[H^+]$ (The substance is a base because it accepts protons). By accepting the H^+ it becomes ionised. If the same substance was placed into a solution with a pH of 9 it would give off the H^+ becoming an unconjungated unionised base.

pKa is a constant however it certainly contributes to the pH of the solution

$$pH = pK_a + \log_{10}\left[\frac{[A^-]}{[HA]}\right]$$

Question 9

Correct answer

b. Glycogen

Marking memorandum

In the absence of oxygen, glycogen is broken down to pyruvate, which is in turn converted to lactic acid. This constitutes the major ATP source for a 400 m sprint.
Hydrolysis of ATP in the cells is essential for the immediate requirement for increased energy supply, but there is only enough ATP stored for 1-2 seconds of work.

Lactate is a metabolite of anaerobic process rather than a source of energy during high intensity activity.

Phosphocreatine contains a high energy phosphate bond similar to ATP and is available in limited supply in muscle for the first 10 seconds at the start of exercise.

Question 10

Correct answer

c. Fatty acid oxidation

Marking memorandum

RER describes the amount of carbon dioxide produced in relation to amount of oxygen used. When the ratio is less than 0.85, ATP is primarily generated from fatty acid metabolism during exercise.

When the majority of ATP generation comes from aerobic glycolysis, RER is above 0.9.

Anaerobic glycolysis (conversion of pyruvate to lactic acid) only occurs during hard exercise in states of critical oxygen supply to the muscle.

Protein is not considered to contribute to energy provision except under conditions of extreme starvation or ultra-endurance performances.

Question 11

Correct answer

b. Has an incidence of 1:3200

Marking memorandum

It has a dibucaine number < 20 and the block duration is 4-8 hours. The incidence of the homozygous silent gene is 1:100000

Question 12

Correct answer

c. The *in vitro* contracture test is the gold standard for the diagnosis of MH

Marking memorandum

There are other receptors implicated such as CACNA1S and STAC3**.** There is no maximum dose. Whatever dose is required. The recommended dose is at least 2 mg/kg

Question 13

Correct answer

b. Drug inactivation by enzymes in the peri-plasmic space

Marking memorandum

Drug inactivation occurs through enzymes that destroy the antibiotic. This is the mechanism of action of b-lactamases and carbapenemases that destroy b-lactams, aminoglycoside-modifying enzymes which inactivate aminoglycosides and chloramphenicol esterases.

Sulphonamides inhibit para-aminobenzoic acid (PABA), an important precursor for the synthesis of folic acid and nucleic acids. Some bacteria do not require PABA and, instead, utilise preformed folic acid. Consequently, such bacteria are sulphonamide resistant.

Efflux pumps. With this mechanism drug is able to penetrate the bacterial cell wall but is immediately pumped back out of the cell. This mechanism is important in the development of tetracyclins. Carbapenem resistant organisms also employ this method, together with porins, but capbapenemases are a bigger problem in our clinical scenario.

Beta-lactam antibiotics work by binding to penicillin-binding proteins within the bacterial cell wall. Bacteria can alter PBPs so that penicillin is unable to bind, a resistance strategy employed by methicillin-resistant S. *aureus*

Question 14

Correct answer

c. The maximum dose that may be used clinically is limited by the toxic effects to the host

Marking memorandum

The maximum dose of aminoglycosides that may be used clinically is limited by toxic effects to the host.

Aminoglycosides rely on concentration-dependant killing of organisms.

Their ability to kill organisms depends on the area below the concentration-time curve. The best way to achieve a large area below the curve is to administer a large dose of antibiotic.

Large infrequent doses of aminoglycosides also minimise toxicity. Aminoglycosids are known for nephrotoxicity and ototoxicity. Uptake into the renal cortex and inner ear is marked with low, sustained concentrations. By giving a once-daily dose, the trough concentration is minimised, resulting in a drug-free period at the end of doing, and reduced toxicity.

Question 15

Correct answer

b. Beta-lactams

Marking memorandum

Beta lactams antibiotics mimics the natural binding substrate for penicillin-binding proteins. They bind to 5-amino acid-peptide chains within the bacterial cell wall so that it cannot be completed, causing death.

Aminoglycosides utilise poring channels to cross the outer bacterial membrane, then penetrate via oxygen dependant, proton pump-coupled mechanisms to bind to the 30S ribosomal subunit, preventing initiation of peptide synthesis and errors in mRNA translation.

Macrolides also inhibit protein synthesis by binding to the 50S subunit of the ribosome to prevent amino acid translocation.

Quinolones inhibit bacterial chromosomal coiling by inhibiting DNA gyrase enzymes

SBA SESSION TWO:
Wiggers Diagram/ Arterial Transducers/ Inotropes

Question 1

Dexmedetomidine should be used with extreme caution in:

a. Elderly patients
b. Patients with renal dysfunction
c. Patients with a fixed cardiac output
d. Patients with opioid withdrawal

Question 2

You are giving a slow intravenous bolus of 1-2 ug dexmedetomidine to a patient for sedation in the MRI suite. You should monitor the patient with special attention to:

a. The saturation as ventilation might be depressed
b. Any signs of an allergic or anaphylactic reaction
c. The blood pressure for hypotension
d. The heart rate for bradycardia

Question 3

A patient with ventricular tachycardia associated with hypotension does not respond to first line treatment and requires amiodarone. Choose the best answer regarding the administration of amiodarone in this situation:

a. The recommended oral starting dose is 800-1600 mg daily in divided doses
b. Amiodarone for infusion should be diluted with dextrose 5% in water to a concentration of 1 - 6 mcg/mL
c. The intra-osseous route is contraindicated
d. Amiodarone should not be administered in patients with porphyria

Question 4

Considering the Vaughan-Williams classification of antiarrhythmic agents, choose the most accurate statement:

a. Lidocaine is a class Ib agent, blocking sodium channels, and increasing the duration of the cardiac action potential
b. Sotalol increases the refractory period by blocking potassium channels
c. Carvedilol is a class II agent and increases the PR and QT intervals
d. Class III and IV agents work mainly by AV node blockade

Question 5

Choose the most appropriate statement, regarding the side-effects of amiodarone therapy:

a. Hypothyroidism is the commonest side effect
b. Copper discoloration of the skin occurs in up to 5% of patients taking amiodarone
c. Pulmonary complications are rare, but may be fatal
d. General anaesthesia may precipitate severe arrhythmias in patients taking amiodarone

Question 6

In the treatment of digoxin toxicity, choose the best answer:

a. Co-administration of NSAIDS can increase the risk of toxicity in patients taking digoxin
b. DigiFab is the first line therapy for digoxin toxicity
c. Haemodialysis should be started early in severe digoxin toxicity
d. Magnesium and Calcium supplementation reduces the risk of toxicity in patients taking digoxin

Question 7

Regarding catecholamines, choose the best answer:

a. Catecholamines are synthesized in the brain
b. Dopamine is a synthetic catecholamine
c. L-Tyrosine is converted to L- Phenylalanine by Tyrosine hydroxylase
d. A catecholamine has a benzene ring with one hydroxyl group and one amine side chain

Question 8

Choose the answer that best describes the effect of the agent on adrenergic receptors:

a. Vasopressin has more α1 than β1 effects
b. Isoproterenol exhibit similar β1 and β2 effects
c. Dobutamine acts mainly on Dopamine receptors
d. Dopamine acts on α1, β1 and Dopamine receptors, but not on β2 receptors

Question 9

Choose the best answer regarding Phosphodiesterase III Inhibitors:

a. Milrinone is used as a first line agent in the treatment of decompensated heart failure
b. Caffeine is an example
c. Milrinone causes vasodilatation and bronchodilation
d. The incidence of arrhythmias as a side effect is not dose related

Question 10

Regarding treatment of intra-operative hypotension with vasopressor drugs:

a. Phenyleprine and Metaraminol exert their effect via direct α1 activity
b. Phenylephrine may be given via topical, subcutaneous, intramuscular or intravenous route
c. Ephedrine undergoes extensive first pass metabolism and is not used orally
d. Ephedrine may increase uterine tone

Question 11

Regarding the physical characteristics of the undamped natural frequency of a catheter-transducer system:

a. For a high undamped natural frequency (UNF), one requires a high stiffness and high effective mass.
b. At the UNF, the distortion of the output amplitude is minimal.
c. At frequencies above the UNF, the output amplitude is reduced.
d. Less energy is required to oscillate an identical mass of fluid in a narrow tube than in a wide tube.

Question 12

With respect to “damping” in a catheter-transducer system:

a. Damping is the dissipation of energy within an oscillating catheter-transducer system, due to frictional resistance.
b. The best trade-off between rapidity of response and accuracy of amplitude occurs when damping is 0.80 of critical.
c. Optimal damping allows accurate recording of the amplitude at the undamped natural frequency.
d. Only when the damping coefficient is 1.0, is the phase lag proportional to the frequency.

Question 13

With respect to the physical principles underlying the intra-arterial measurement of blood pressure:

a. Pressure is the work done per unit area.
b. Force is that which changes the state of rest or motion of a body.
c. All complex wave forms can be resolved into a series of cosine waves.
d. The fundamental frequency of the arterial pressure wave form plus ten harmonics is approximately 100 Hz.

Question 14

With an acute afterload increase of 20mm Hg, the stroke volume of the RV and LV will:

a. Decrease by 10 % in both the RV and LV
b. Increase in the LV but decrease in the RV
c. Decrease by 10 % in the LV and 30% in the RV
d. Increase by 20 % in the LV and the RV

Question 15

Rapid infusion of a colloid that increases the RV volume from 75 ml to 200 ml will result in:

a. RV failure
b. RV systolic pressure increase from 25mm Hg to 40mm Hg
c. RV end diastolic pressure increase from 5mm Hg to 40mm Hg
d. RV systolic pressure increase from 10mm Hg to 25mm Hg

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Answers

Question 1

Correct answer

c. Patients with a fixed cardiac output.

Marking memorandum

The bradycardia and initial peripheral vasoconstriction would cause a dramatic fall in cardiac output. The myocardium might be dependent on a catecholamine drive and the reduced sympathetic outflow will be detrimental.

a. The pharmacokinetics of dexmedetomidine is minimally affected by age.
b. The kinetics of dexmedetomidine is unchanged in patients with renal failure. It undergoes complete biotransformation in the liver and metabolites are inactive. There could be a theoretical accumulation of inactive metabolites in patients with severe renal failure.
c. Correct answer
d. Alpha 2 agonists are used for the treatment of opioid and alcohol withdrawal as it reduces the hyperdynamic state and increased catecholamine outflow associated with withdrawal.

Question 2

Correct answer

d. Monitor the heart rate for bradycardia

Marking memorandum

The initial bradycardia is a baroreceptor response secondary to hypertension due to direct peripheral post synaptic alpha 2B stimulation. This response can be avoided by slower administration of the initial bolus.

a. Alpha 2 agonists have the advantage of not causing respiratory depression on their own.
b. An allergic or anaphylactic response to alpha 2 agonists is extremely rare and less than a handful of mild skin reactions have been documented.
c. Initial peripheral post synaptic alpha 2B stimulation, as occurs during bolus dose administration, causes a hypertensive response. After 10-30 minutes, decreased sympathetic outflow leads to mild hypotension.

Question 3

Correct answer

d.

Marking memorandum

a. Yes, but intravenous administration is more appropriate in a haemodynamically unstable patient
b. It should be diluted with dextrose 5% in water to a concentration of 1 - 6 **mg**/mL
c. The IO route may be used in emergencies
d. True

Question 4

Correct answer

b.

Marking memorandum

a. It decreases the duration of the AP
b. True
c. It increases PR interval only
d. Class II and IV agents mainly block the AV node

Question 5

Correct answer

d.

Marking memorandum

a. It only occurs in 2-4%
b. Blue-grey discolouration can occur, rarely
c. Pulmonary complications are very common (10-17%)
d. True, it may cause severe bradycardia resistant to medical treatment, requiring pacing

Question 6

Correct answer

a.

Marking memorandum

a. True, it increases plasma digoxin levels
b. It is only reserved for severe toxicity
c. Haemodialysis is not very effective in the treatment of digoxin toxicity and is not routinely used
d. Calcium increases the risk of toxicity

Question 7

Correct answer

a.

Marking memorandum

a. True, catecholamines are synthesized in the brain, adrenal medulla and postganglionic sympathetic nerve fibres
b. Dopamine is a naturally occurring catecholamine
c. L-Tyrosine is converted to L-Dihydroxyphenylalanine (L-DOPA) by Tyrosine hydroxylase, this is the rate-limiting step in the production chain
d. A catecholamine has a benzene ring with two hydroxyl groups and one amine side chain

Question 8

Correct answer

b.

Marking memorandum

a. Vasopressin does not affect adrenergic receptors, it acts on vasopressin receptors
b. True
c. Dobutamine acts on α1, β1 and β2 receptors, not Dopamine receptors
d. Dopamine has β2 activity as well

Question 9

Correct answer

d.

Marking memorandum

a. Milrinone is used as a second-line agent in the treatment of decompensated heart failure
b. Caffeine is a nonselective PDE inhibitor
c. Milrinone causes vasodilatation, but may cause bronchospasm
d. True, the incidence of arrhythmias is not dose-related, both supra- and ventricular arrhythmias may occur at very small doses

Question 10

Correct answer

b.

Marking memorandum

a. Metaraminol has direct and indirect actions, with some β activity
b. True
c. Ephedrine is rapidly and completely absorbed and can be given orally
d. Ephedrine decreases uterine tone

Question 11

Correct answer

c.

Question 12

Correct answer

a.

Question 13

Correct answer

b.

Question 14

Correct answer

c.

Marking memorandum

a. The decrease in SV is felt far more in the RV than the LV
b. An increase in preload will increase SV in both ventricles
c. Correct answer- The RV cannot cope well with an increase in afterload as it is thin walled.
d. An increase in preload will result in increased SV

Question 15

Correct Answer

b.

Marking memorandum

a. The right ventricle can increase in volume with ease. An acute increase in pressure will result in RV failure
b. Correct answer
c. Normal RV pressures are 25/5 mm Hg. Diastolic pressure will only increase slightly: 10 mmHg
d. Normal RV pressures are 25/5 mm Hg.

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SBA SESSION THREE:
Calcium, Magnesium, Phosphate, Pacemakers, Electricity

Question 1

A 70-kg adult contains approximately 1300g of calcium (Ca^{2+}). Concerning the distribution of this important electrolyte:

a. 40-50% of the circulating Ca^{2+} (approximately 1% of total) is protein bound and considered physiologically active
b. 40-50% of the circulating Ca^{2+} (approximately 1% of total) is protein bound primarily to albumin
c. 99% of Ca^{2+} is deposited in bones and teeth and mostly bound to bisphosphonate that is necessary for structural integrity.
d. In bone there is a large pool of about 25000 mmol Ca^{2+} readily available for rapid exchange to the fluid compartments,

Question 2

Serum Ca^{2+} concentration is determined to some extent by protein concentration. Its level is also influenced by blood pH. Choose the correct statement:

a. Alkalosis decreases free Ca^{2+} levels
b. Changes in total Ca^{2+} levels are physiologically important as it is the biologically active form
c. Corrected Ca^{2+} = 20 x measured [Ca] / (40 - [albumin])
d. Normal calcium levels: 2mmol/L (ionised) + 1mmol/L (protein-bound) = 3mmol/L

Question 3

The major effector organs in Ca^{2+} homeostasis are bones, kidneys and intestines. Their participation in Ca^{2+} regulation is facilitated by hormones with unique effects. Choose the correct statement:

a. PTH acts on the kidneys to increase calcium excretion at the thick ascending limb. Additionally, it also potentiates the formation of Vit D3 from 1, 25–dihydroxycholecalciferol in the renal tubules.
b. PTH causes increased bone deposition through increased osteoblast activity
c. Calcitonin is released from parafollicular C cells of the thyroid gland. It counters the effects of PTH (Parathyroid hormone)
d. Calmodulin works upon the GIT to indirectly increase Ca^{2+} reabsorption

Question 4

With regard to magnesium, choose the correct statement:

a. It is the most plentiful cation in the human body
b. Hypermagnesaemia may cause hypertension, hyper-reflexia and indirectly cause hypocapnia
c. Mg^{2+} is an essential regulator in chloride access in the cell and the actions of chloride within the cell
d. It is essential for the production and function of ATP

Question 5

Pertaining to phosphate, choose the correct statement:

a. The refeeding syndrome is associated with hyperphosphataemia
b. Rapid increase in serum phosphate can lead to the development of severe hypocalcaemia
c. Hypophosphataemia can occur after tissue damage or cell death, moderate to severe renal failure or haematological malignancies associated with high cell turnover
d. In the kidney PTH promotes proximal tubular phosphate reabsorption and decreases its renal excretion.

Question 6

Regarding transformers:

a. In a step-up transformer, the voltage across the secondary coil is greater than the voltage across the primary coil.
b. In a step-down transformer, the output power is greater than the input power.
c. In a step-down transformer, there are fewer turns on the primary coil than the secondary coil
d. Transformers are based on the principles of conductance to adjust levels of current and voltage

Question 7

Choose the incorrect statement: if an electric current is fed through the body:

a. risk of injury is largely dependent upon the current flow
b. antistatic shoes provide good protection due to their high resistance
c. ventricular fibrillation occurs at a lower current in patients with dysrrhythmias
d. high frequencies are more dangerous than low frequencies

Question 8

Regarding capacitors:

a. Capacitors used in defibrillators typically have a capacitance of ≥1 farad.
b. Increasing the distance between the plates of a capacitor increases its capacitance.
c. The maximum amount of charge (Q) that a capacitor can store is proportional to the battery voltage (V) that supplies it.
d. The stored energy of a capacitor is given by the formula: $E = \frac{1}{2}QV^2$.

Question 9

The proper response to a line isolation monitor (LIM) alarm is to:

a. Shut off power to the operating room
b. Report it in the Surgical Safety Checklist
c. Notify the municipality that there is a grounding problem
d. Unplug equipment one item at a time, starting with the last item plugged in

Question 10

Microshock occurs:

a. In the electrically susceptible patient
b. When small currents are delivered over hours
c. In most microsurgical procedures
d. When a transformer has failed

Question 11

The dispersive pad for an electrosurgical unit:

a. Should be placed over a hairy part of the body
b. Should be placed over a patient's total hip replacement
c. Should be placed over a well-muscled area such as the thigh
d. Is not necessary most of the time

Question 12

The cardiac glycoside, digoxin, increases myocardial contractility by which of the following mechanisms?

a. Stimulation of Na^+-K^+-ATPase
b. Inhibition of Na^+-K^+-ATPase
c. Activation of phospholipase C
d. Phosphorylation of L-type calcium channels

Question 13

Stimulation of β1 receptors in the heart results in increased rate and force of cardiac contraction. Which of the following statements best describes the mechanism of action of these G-protein coupled receptors?

a. α-GDP activates phospholipase C (PLC) resulting in increases in intracellular inositol 1,4,5-triphosphate (IP_3)
b. α-GTP activates phospholipase C (PLC) resulting in increases in intracellular inositol 1,4,5-triphosphate (IP_3)
c. α-GDP activates adenylyl cyclase resulting in increases in intracellular cyclic adenosine 3',5'-monophosphate (cAMP)
d. α-GTP activates adenylyl cyclase resulting in increases in intracellular cyclic adenosine 3',5'-monophosphate (cAMP)

Question 14

Bradycardia is mediated by acetylcholine at which of the following muscarinic receptor subtypes?

a. M1
b. M2
c. M3
d. M4

Question 15

The nicotinic acetylcholine receptor is a pentameric ligand-gated ion channel. Acetylcholine binding sites are located on which 2 subunits?

a. α and α
b. α and β
c. α and γ
d. α and δ

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Answers

Question 1

Correct answer

b. 40-50% of the circulating Ca^{2+} (approximately 1% of total) is protein-bound, primarily to albumin

Marking Memorandum

Circulating calcium:
1% of total calcium exists in blood
40-50% protein bound (primarily albumin) and not filtered by glomerular capillaries
50% ionized (physiologically active) and filtered at the glomerular membrane
10% non-ionized, and chelated with phosphate, sulphate and citrate. Complexed to organic proteins.

50% of the circulating calcium (approximately 1% of total) is ionized and this is considered physiologically active

99% of Ca^{2+} is found in bones and teeth and most bone calcium bound to hydroxyapatite, necessary for structural integrity

There is a small pool of exchangeable calcium of about 100mmol within bone that can be readily exchanged. Most of the calcium in bone (25000mmol) is in a stable state that is slowly exchanged through reabsorption.

Question 2

Correct answer

a. Alkalosis decreases free Ca^{2+} levels

Marking Memorandum

Acidosis decreases the amount of calcium bound to albumin and therefore increases free calcium. Alkalosis, conversely, increases the protein binding of calcium and thereby decreases the free fraction of calcium.

Ionized Ca^{2+} is the essential active form and change to its concentration has major physiological impact. Total calcium levels are less influential.

When ionized calcium cannot be measured directly with the use of calcium-specific electrodes the approximate amount of calcium bound to protein is given by the following equation:
Corrected [Ca] = measured [Ca] + {(40 - [albumin]) * 0.02}

NORMAL Ca VALUES (mmol/l)

	Lower Limit	Upper Limit
Ionized	**0.96**	**1.2**
Protein bound	**1.10**	**1.74**
Total	**2.30**	**2.70**

Question 3

Correct answer

c. Calcitonin is released from parafollicular C cells of the thyroid gland. It counters the effects of PTH (parathyroid hormone).

Marking Memorandum

Calcitonin is released from parafollicular C cells of the thyroid gland. It is released in response to hypercalcaemia. It counters the effects of PTH (parathyroid hormone) but has little effect on long-term calcium homeostasis.

The effect of PTH on the kidney is to increases calcium reabsorption at the thick ascending limb. Within the renal tubules - PTH potentiates the formation of Vit D3 (calcitriol)
25OHD3 → 1α hydroxylase → 1,25-dihydroxycholecaciferol (1,25 OH2D: vitamin D3 active form)

Bone acts as the body's major reservoir of calcium. PTH release (in response to decreased calcium levels) bone reabsorption occurs through increased osteoclastic/decreased osteoblastic activity, and calcium is released.

Calcitriol (Vit D3) indirectly acts upon the GIT, increasing Ca^{2+} reabsorption from the intestines. This is potentiated by the release of PTH.

Question 4

Correct answer

d. It is essential for the production and function of ATP

Marking Memorandum

ATP is only fully functional (biologically active) when chelated to Mg (what is called ATP is often actually Mg-ATP). As such, magnesium plays a role in the stability of all polyphosphate compounds in the cells, including those associated with the synthesis of DNA and RNA.

Magnesium is the fourth most plentiful cation while K^+ is the most plentiful cation

Magnesium causes vasodilation→ hypotension; muscle weakness and hyporeflexia, and ultimately respiratory impairment that will lead to hypercapnia

Mg^{2+} is an essential regulator of Ca^{2+} access into the cell and its actions within the cell. It may be regarded as a natural physiological Ca^{2+} antagonist.

Question 5

Correct answer

b. Rapid increase in serum phosphate can lead to the development of severe hypocalcaemia

Marking Memorandum

Rapid increase in serum phosphate can lead to the development of severe hypocalcaemia.
This occurs secondary to decreased calcitriol (vitD3) production, leading to a decline in GIT calcium absorption. Frank precipitation of Ca^{2+} and PO^{4-} also contributes to decreased Ca^{2+}.

Many intracellular minerals become severely depleted during fasting/malnourished state although serum levels remain normal. Insulin secretion is suppressed in this fasted state and glucagon secretion is increased. During re-feeding, insulin secretion resumes in response to increased blood sugar, resulting in increased glycogen, fat and protein synthesis. This process requires phosphates, magnesium and potassium (which are already depleted) and the stores rapidly become used up.

Formation of phosphorylated carbohydrate compounds in the liver and skeletal muscle depletes intracellular ATP and 2,3-diphosphoglycerate in red blood cells, leading to cellular dysfunction and inadequate oxygen delivery to the body's organs. Intracellular movement of electrolytes occurs along with a fall in these electrolytes, including phosphorus and magnesium.

Hyperphosphataemia can occur after tissue damage or cell death, moderate to severe renal failure or haematological malignancies associated with high cell turnover.

PTH inhibits proximal tubular inorganic phosphate reabsorption and increases excretion.

Question 6

Correct answer

c. In a step-down transformer, there are fewer turns on the primary coil than the secondary coil.

Marking Memorandum

Step up transformers increase the voltage in the secondary coil
In a step-down transformer, there are more turns on the primary coil. Output power is decreased.
Transformers use the principle of induction

Question 7

Correct answer

d. high frequencies are more dangerous than low frequencies

Question 8

Correct answer

c. The maximum amount of charge (Q) that a capacitor can store is proportional to the battery voltage (V) that supplies it.

Marking Memorandum

1 farad is a very large amount of capacitance. Most capacitors have much smaller values.
The capacitance is inversely proportional to the distance between the plates
Stored energy $E = ½ CV^2$ where C is capacitance. Q related to charge.

Question 9

Correct answer

d. Unplug equipment one item at a time, starting with the last item plugged in

Marking Memorandum

The LIM alarms when it has detected a current leakage in an isolated power supply above its alarm threshold. The most common reason is one or more devices connected to the power supply have a ground fault. To determine which device has the fault, disconnect each device from the power supply, one at a time, until the alarm stops.

Question 10

Correct answer

a. In the electrically susceptible patient

Marking Memorandum

Very small amounts of current below the threshold of perception are generally not harmful to patients; however, when a patient has a direct conductive connection to the heart (e.g., saline-filled vascular catheter or a pacing wire), the current may be sufficient to induce an arrhythmia. When this happens, the patient has received a microshock.

Question 11

Correct answer

c. Should be placed over a well-muscled area such as the thigh

Marking Memorandum

The dispersive pad is an important piece of equipment to allow return of electrical currents from an electrosurgery unit. Good contact of the dispersive pad and a large surface area lower the current density and impedance to return of the current. Poor contact with the skin (e.g., dry gel, hairy body,

incomplete contact from poor application) can all increase the impedance and reduce the area through which the current returns, thus increasing the current density. Patients may suffer burns if the current density is high enough. Bony prominences or metal objects in the patient can also concentrate the current, causing heating or burning.

Question 12

Correct answer

b. Inhibition of Na^+-K^+-ATPase

Marking memorandum

Digoxin *inhibits* Na^+-K^+-ATPase that has particular importance in the heart, where the Na^+-K^+ exchange is replaced by Na^+-Ca^{++} exchange. This results in increased intracellular calcium that increases myocardial contractility

Digoxin has no effect on the Gq-protein coupled receptors that activate PLC resulting in increased intracellular calcium via IP3

Digoxin has no effect on the Gs-protein coupled receptors whose activation result in an increase in intracellular cAMP. In the heart, cAMP activates a specific PKA that phosphorylates several important cardiac ion channels including L-type calcium channels.

Question 13

Correct answer

e. α-GTP activates adenylyl cyclase resulting in increases in intracellular cAMP

Marking memorandum

β_1 receptors are Gs-protein coupled receptors. Activation of PLC/IP_3 is not the mechanism of action at β_1 receptors
α-GTP (not GDP) activates adenyl cyclase

Question 14

Correct answer

a. M2

Marking Memorandum

M2 Gi-protein coupled receptors in the heart control cardiac myocyte contractility resulting in slowing of the heart rate, reduced contractile force of the atrium, and reduced conduction velocity of the AV node

M1 Gq-protein coupled receptors located in the autonomic ganglia, salivary glands and stomach. They predominate in the CNS, being found in the hippocampus, cerebral cortex, and striatum. The functioning of these receptors is critical for memory processes.

M3 Gq-protein coupled receptors with widespread location, no significant effect on the heart

M4 Gi-protein coupled receptors located in the CNS where overall effects are inhibitory

Question 15

Correct answer

a. α and α

Marking Memorandum

nAchR is a pentameric ligand-gated ion channel. The 5 subunits (2 α, and one β, δ and ε or γ) span the entire membrane and create a central pore. Ach is the endogenous ligand and binding sites are located on the 2 α subunits; both of which need to be bound to Ach to trigger conformational change which 'opens' the pore and allows for the influx of calcium and sodium ions, and the efflux of potassium. The α subunit is also the binding site of acetylcholine receptor agonists and antagonists.

SESSION FOUR:
Haldane/Bohr/Control of breathing/Breathing systems/Pulmonary physiology/OHDC

Question 1

Increases in the carbon dioxide partial pressure of blood or decreases in blood pH result in a lower affinity of haemoglobin for oxygen. This is best described by which of the following phenomena?

a. Bohr effect
b. Double Bohr effect
c. Double Haldane effect
d. Haldane effect

Question 2

Which of the following statements best describe the impact of the Bohr effect on the oxyhaemoglobin dissociation curve?

a. Rightward shift of the oxyhaemoglobin dissociation curve with resultant decrease in affinity of haemoglobin for oxygen
b. Rightward shift of the oxyhaemoglobin dissociation curve with resultant increase in affinity of haemoglobin for oxygen
c. Leftward shift of the oxyhaemoglobin dissociation curve with resultant decrease in affinity of haemoglobin for oxygen
d. Leftward shift of the oxyhaemoglobin dissociation curve with resultant increase in affinity of haemoglobin for oxygen

Question 3

Which of the following statements most accurately pertains to the Haldane effect?

a. Deoxyhaemoglobin has a higher affinity for carbon dioxide than oxyhaemoglobin resulting in the formation of carbamino compounds which account for approximately 70% of the Haldane effect
b. The increased buffering capacity of deoxyhaemoglobin and transport of carbon dioxide as bicarbonate accounts for approximately 90% of the Haldane effect
c. The Haldane effect accounts for approximately 50% of the carbon dioxide excreted by the lungs and is physiologically less important than the Bohr effect
d. Deoxyhaemoglobin has a higher affinity for carbon dioxide than oxyhaemoglobin resulting in the formation of carbamino compounds which account for approximately 6% of the Haldane effect

Question 4

On a graph with $PaCO_2$ on the x axis and minute ventilation on the y axis, a left shift or steepening of the CO_2 response curve can be caused by:

a. Hypoxaemia
b. Sleep
c. Metabolic alkalaemia
d. Inhalational anaesthetic agents

Question 5

The most important variable in the control of breathing under normal circumstances is the effect of:

a. Arterial PCO_2 on the central chemoreceptors
b. Arterial PO_2 on the central chemoreceptors
c. Arterial pH on the central chemoreceptors
d. Arterial hydrogen ion concentration on the central chemoreceptors

Question 6

Which of the following is most often associated with an increased affinity of haemoglobin for oxygen?

a. Acute ascent to high altitude
b. Chronic anaemia
c. Intense exercise
d. Blood transfusion

Question 7

Red blood cells are removed by the reticuloendothelial system and their haemoglobin content is recycled. The protoporphyrin ring is cleaved and excreted in bile as which of the following

a. Bilirubin
b. Biliverdin
c. Stercobilin
d. Urobilinogen

Question 8

Foetal haemoglobin (HbF)

a. Has a P50 of 28 mmHg
b. Is the main oxygen transport protein in children up to the age of 6 years
c. Causes a left shift in the O2 dissociation curve
d. In most adults, at least 15% of Hb is HbF.

Question 9

Regarding HbF:

a. NIRS analysis is significantly different in neonates (HbF) and older children and adults (HbA)
b. Higher levels of HbF (>10%) in older children and adults is associated with a milder form of sickle cell disease
c. HbF is the first and only form of haemoglobin synthesised during gestation
d. Histidine and serine are both negatively charged

Question 10

The oxygen haemoglobin dissociation curve has a sigmoidal shape; this feature of the curve is because

a. Haem is formed by 4 pyrrole molecules that forms a porphyrin ring and is bound to iron
b. Haemoglobin has a quaternary structure that allows each molecule to bind up to 4 oxygen molecules
c. The allosteric property of haemoglobin increases the affinity with which each oxygen molecule binds to each remaining haem group
d. The most common form of Haemoglobin is HbA which is made up of 2 alfa and 2 beta chains

Question 11

A critically ill patient with ARDS is ventilated in the ICU and presents with the following arterial blood gas: (Fi02 60%)

pH 7.16
PCO2 7.51 kPa
PO2 10.5 kPa

Lactate 1.6mmol/L
Hb 10.6 g/dl
p50 4.26 kPa (31.9mmHg)
SaO2 93%
BE -7mmol/L
HCO_3^- 18.6mmol/L

Which of the following statements best describes this arterial blood gas

a. The p50 of this patient is moved to the right
b. The p50 of this patient is moved to the left
c. The affinity of Haemoglobin to oxygen is increased so more oxygen can be taken up as critically ill patients require more oxygen
d. The p50 is a measured parameter

Question 12

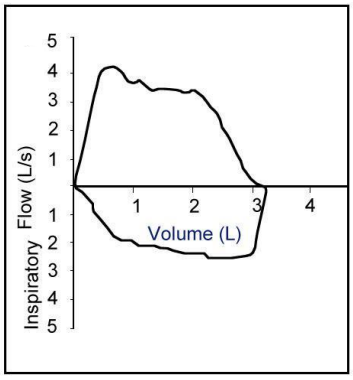
What do you understand by static and dynamic compliance of the lung?

a. Compliance is highest at high lung volumes.
b. Dynamic compliance measurement is influenced by regional lung elasticity and airway resistance.
c. Dynamic compliance is measured during periods of breath-holding.
d. Static compliance is defined as pressure gradient change per lung volume change.

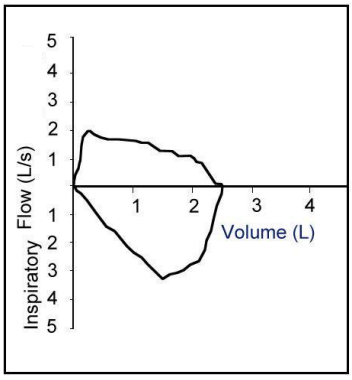
Question 13

Indicate which statement most accurately describes its corresponding diagram:

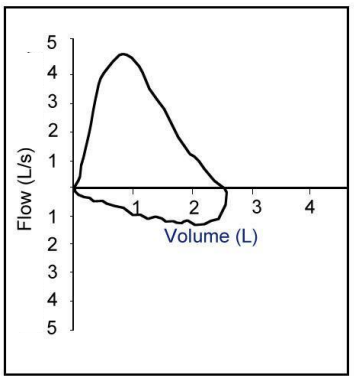
a)



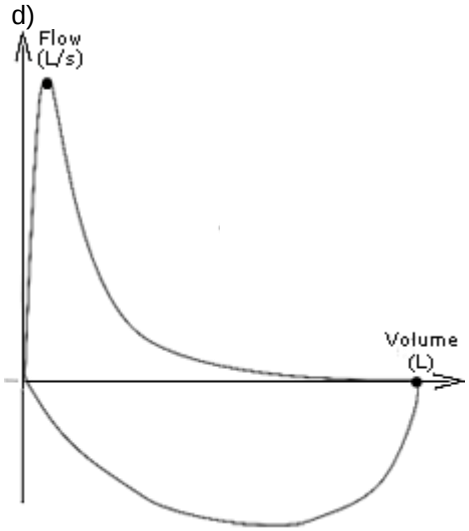
b)



c)

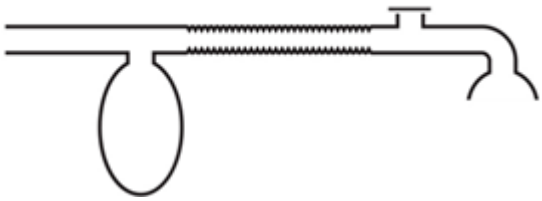


d)



a. Is compatible with fixed upper airway intrathoracic obstruction.
b. Represents variable extrathoracic upper airway obstruction.
c. Represents variable intrathoracic upper airway obstruction.
d. Is suggestive of restrictive lung disease.

Question 14



This circuit is a:

a. Mapleson A
b. Mapleson B
c. Mapleson C
d. Not part of the Mapleson classification

Question 15

For a circle system to be efficient three of the following are essential:

A) The fresh gas inflow cannot enter the circuit between the expiratory valve and the patient
B) The soda lime canister must have a volume half that of the patients tidal volume.
C) A unidirectional valve must be located between the patient and the reservoir bag on both the inspiratory and the expiratory limb
D) The overflow/ APL valve cannot be located between the patient and the inspiratory valve.

The correct combination of three statements is

a. ABC
b. ACD
c. BCD
d. ABD

Answers

Question 1

Correct Answer

a. Bohr effect

Marking memorandum

a. Bohr effect (correct answer) Increases in the carbon dioxide partial pressure of blood or decreases in blood pH results in a lower affinity of haemoglobin for oxygen. This favours oxygen delivery to the tissues where CO_2 is high.

b. Double Bohr effect: Refers to pregnancy, when CO_2 passes from fetal to maternal blood at the placenta causing maternal blood CO_2 to rise (R shift of the OHDC and reduced oxygen affinity), and the fall in fetal blood CO_2 shifts the curve to the L with increased oxygen affinity. Net effect is to favour oxygen transfer from maternal to fetal blood.

c. Double Haldane effect- incorrect

d. Haldane effect: The increased capacity of deoxygenated blood for CO_2 transport compared with oxygenated blood.

Question 2

Correct answer

a. Rightward shift of the oxyhaemoglobin dissociation curve with resultant decrease in affinity of haemoglobin for oxygen

Marking memorandum

Explanation of the Bohr effect: The decrease in oxygen affinity of haemoglobin that occurs when the pH of blood falls/CO_2 increases. A rightward shift results in an increased P50, and thus a higher PO_2 is required for haemoglobin to bind a given amount of oxygen.

Question 3

Correct answer

a. Deoxyhaemoglobin has a higher affinity for carbon dioxide compared to oxyhaemoglobin resulting in the formation of carbamino compounds which account for approximately 70% of the Haldane effect

Marking Memorandum

a. True statement: Increased formation of carbamino compounds accounts for two-thirds of the Haldane effect, with the remainder being a result of the greater buffering capacity of deoxyhaemoglobin.

b. The buffering capacity of deoxyhaemoglobin and transport of carbon dioxide as bicarbonate accounts for a minimal percentage of the Haldane effect. Approximately 90% of the carbon dioxide in blood is in the form of bicarbonate ions.

c. The Haldane effect is physiologically MORE important than the Bohr effect in the lungs

d. The initial segment is true as it is in the answer, but this effect accounts for < 70% of the Haldane effect. Carbamino compounds account for approximately 6% of CO2 transport in blood.

Question 4

Correct answer

a. Hypoxaemia

Marking Memorandum

Hypoxaemia and metabolic acidosis cause a left shift (increase in minute ventilation) of the CO_2 response curve.

Sleep, metabolic alkalaemia and inhalational anaesthetic agents cause a right shift of the curve (hypoventilation)

Question 5

Correct answer

a. Arterial PCO_2 on the central chemoreceptors

Marking Memorandum

The main response to an increase in arterial PCO_2 comes from the central medullary chemoreceptors in response to the increase in H^+ ions in the CSF/ECF. About 20% of the response comes from the peripheral chemoreceptors stimulated by the increased arterial PCO_2 and arterial pH. Hypoxia makes the individual more sensitive to increases in arterial PCO_2. The peripheral chemoreceptors are responsible for the ventilatory response to hypoxia.

Question 6

Correct Answer

d. Blood transfusion

Marking Memorandum

d. Blood transfusion (correct answer)
Blood stored for transfusion in SAGM for up to 14 days has decreased amounts of 2,3-DPG resulting in a leftward shift in the oxyhaemoglobin dissociation curve and thus reduced oxygen delivery to the tissues for up to 24 hours after the transfusion.

a. Acute ascent to high altitude (distractor)
Altitude triggers a significant rise in levels of 2,3-DPG and right shift of the OHDC and a reduced affinity of haemoglobin for oxygen; opposed by the rise in pH (respiratory alkalosis) after about 6 hours at altitude.

b. Chronic anaemia (distractor)
Anaemia (and many other diseases in which there is chronic hypoxia) results in an increase in 2,3-DPG and right shift of the OHDC and a reduced affinity of haemoglobin for oxygen.

c. Intense exercise (distractor)
Exercise results in increased 2,3-DPG & right shift of the OHDC, also fuelled by temperature rise in active tissues and accumulation of CO_2 and metabolites. The same effect may not occur in the trained athlete.

Question 7

Correct Answer

a. Bilirubin

Marking Memorandum

a. Bilirubin
Bilirubin is transported to the liver bound to albumin where it is conjugated with glucoronic acid allowing for excretion in bile
b. Biliverdin
The protoporphyrin ring is cleaved to form biliverdin which is then reduced to bilirubin which is excreted in bile as outlined above
c. Stercobilin

Bilirubin is converted to stercobilin in the gut

d. Urobilinogen
Some of the stercobilin in the gut is absorbed and excreted by the kidneys as urobilinogen

Question 8

Correct answer

c. Causes a left shift in the O2 dissociation curve

Question 9

Correct answer

a. Higher levels of HbF (>10%) in older children and adults is associated with a milder form of sickle cell disease

Question 10

Correct answer

a. Haemoglobin is an allosteric molecule that is responsible for the change in affinity after each of the 4 possible oxygen molecules bind and each successive molecule binds easier than the previous one.

Marking Memorandum

a. Haem is formed by 4 pyrrole molecules that forms a porphyrin ring and bound to iron in the Ferrous state, but this is not a quality responsible for the sigmoid shape of the curve
b. Haemoglobin is a quaternary structure that allows each molecule to bind up to 4 oxygen molecules but the molecule changes with the binding of each oxygen molecule that gives it it's unique properties
b. Haemoglobin A is made up of 2 alpha and 2 beta chains but not primary reason for the sigmoid shape of the curve

Question 11

Correct answer

a. The p50 is moved to the right. In an acidotic state, with tissue hypoxia, oxygen release will be enhanced, to facilitate its delivery to metabolically challenged areas.

Marking Memorandum

b. Normal p50 is 3,5 kPa and on the bloodgas the p50 is 4,26 which is more and the curve is thus not moved to the left
c. Haemoglobin's affinity for oxygen is decreased, oxygen release is enhanced to facilitate its delivery to hypoxic areas
d. p50 is a calculated parameter

Question 12

Correct answer

a. Dynamic compliance measurement is influenced by regional lung elasticity and airway resistance.

Marking Memorandum

Dynamic compliance is measured during normal tidal breathing, so in patients with abnormal dynamic compliance, not only will the measurement be influenced by changes in elasticity, but also by differing alveolar time constants. This means that although there is no flow at the mouth when the measurement is made, there will be intrapulmonary flow at this time, which is influenced by airway resistance.

Question 13

Correct answer
a. Is compatible with fixed upper airway intrathoracic obstruction.

Marking Memorandum
b and c are clearly transposed, and d is clearly an example of obstructive lung disease.

Question 14

Correct answer
a. Mapleson A

Question 15

Correct answer
a. ACD

SBA SESSION FIVE:
Statistics; Elementary mathematics

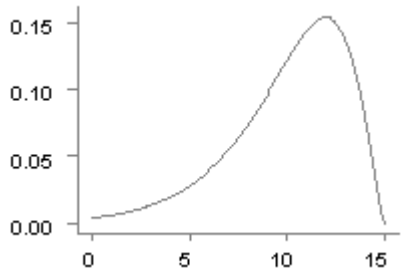
Question 1:

Which one of the following is not an indicator of *data spread*?

a. Variance
b. Interquartile range
c. Average
d. Standard deviation

Question 2:

The curve below can be described as:



a. Bimodal
b. Positively skewed unimodal
c. Skewed to the left unimodal
d. Symmetrical unimodal

Question 3:

Which of the following is not always a feature of the *normal distribution curve*?

a. The mean μ = 0
b. Approximately 68% of the data set falls within one standard deviation from the mean
c. Approximately 95% of the data set falls within two standard deviations from the mean
d. The curve is symmetrical

Question 4:

		The "Truth"	
		Yes	No
Test Result	Yes	(A) True +	(B) False +
	No	(C) False –	(D) True –

With reference to the table above, which one of the following statements is incorrect?

a) Sensitivity is the ability of a test to detect the true positive rate or A/A+C
b) Specificity is the ability of a test to correctly identify persons with the disease or B/B+C
c) The Positive predictive value is the probability that subjects with a positive screening test truly have the disease or A/A+B
d) Negative predictive value is given by the value D/C+D

Question 5:

	Reject	Accept
H_0 True	a	b
H_0 False	c	d

Question: With reference to the truth table above which area reflects the *Type 1 error*?

a. Area labelled “a”
b. Area labelled “b”
c. Area labelled “c”
d. Area labelled “d”

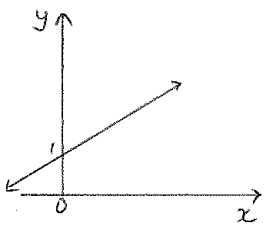
Question 6:

Which one of the following equations is incorrect?

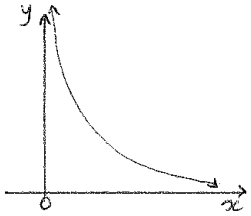
a. $e^0 = 1$
b. $Log_2 (64) = 6$
c. $Log_8 (0.125) = -1$
d. $10^0 = 10$

Question 7:

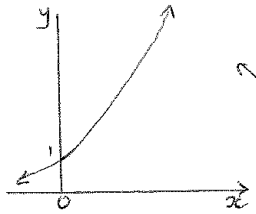
Which of the following graphs represents the inverse function y = $\frac{1}{x}$?



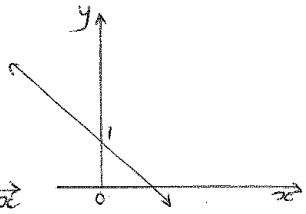
Graph A



Graph B



Graph C



Graph D

a. Graph A
b. Graph B
c. Graph C
d. Graph D

Question 8:

Tests for *statistical heterogeneity*, such as Cochran's Q-statistic and the I^2-statistic, are commonly used in meta-analyses to determine:

a. Whether there are genuine differences underlying the results of the studies
b. Whether the variation in findings is compatible with chance alone
c. Both A and B
d. Neither A nor B

Question 9:

Measures which provide information regarding the relative position of other data points in a sample include range, inter-quartile range, standard deviation, standard error of the mean (SEM). These are examples of:

a. Variability
b. Efficacy
c. Efficiency
d. Neither

Question 10:

The option which describes *variability* is:

a. Variability is calculated by subtraction between the highest and lowest values from a set of data
b. The total range of a variable is the distance between the highest and lowest values
c. Mathematically, the square root of the variance is the standard deviation
d. All of the above

Question 11:

A clinical trial is conducted to see if treating anaemic patients with oral iron medications enhances patients' perioperative outcome. A *Type I error* is to:

a. Claim oral iron does not enhance patient outcome when it does
b. Claim oral iron enhances patient outcome when it does not
c. Claim oral iron does not enhance patient outcome
d. Claim oral iron enhances patient outcome

Question 12:

In a statistical test of hypotheses, a *Type II error* is committed if:

a. We reject the null hypothesis when, in fact, the null hypothesis is valid.
b. We fail to reject the null hypothesis when, in fact, the null hypothesis is valid.
c. We fail to reject the null hypothesis when, in fact, the null hypothesis is invalid.
d. We reject the null hypothesis when, in fact, the null hypothesis is invalid.

Question 13:

A *power analysis* allows for detecting:

a. The probability of appropriately accepting the null hypothesis if it is false.
b. The probability of appropriately rejecting the null hypothesis if it is false.
c. The probability of appropriately accepting the null hypothesis if it is true.
d. The probability of appropriately rejecting the null hypothesis if it is true.

Question 14:

A study has collected the number of patients with blood groups, A/B/AB/O undergoing anaesthesia. This data is an example of:

a. Binomial data
b. Ordinal data
c. Nominal data
d. Interval data

Question 15:

A randomised controlled study involves two groups: the control, and the treatment group. Randomly assigning patients allows for:

a. An increased probability that differences in the groups can be attributed to the treatment.
b. A reduced risk of bias.
c. Both
d. Neither

Answers

Question 1

Correct answer:

b. Average

Marking memorandum:

a. Distractor: Variance is the distance of the data points from the mean. It is calculated from the sum of squares of the deviation from the mean so is an indicator of spread.
b. Distractor: Interquartile range gives the values at the lower and at the higher bounds of the data in a particular 25% of the full range and is therefore an indicator of spread of data.
c. Correct answer: The average is the arithmetic sum of the data values divided by the number of values. E.g. the average of 3 can be obtained by data where all the values are 3,3,3,3,3 or from the values of 1, 2, 3, 4 ,5. The first group of data has no spread whereas the second is clearly spread more widely.
d. Distractor: The standard Deviation is the square root of the variance which makes it an indicator of data spread.

Question 2

Correct answer:

c. The curve is unimodal and the long tail is to the left.

Marking memorandum:

a. Distractor: The curve does not have two peaks so is not bimodal. i.e. there are not two modes (with the mode being the data value occurring most frequently in the set).
b. Distractor: The curve has one peak so is unimodal but the long tail is to the left. A positively skewed curve has a long tail to the right.
c. Correct answer: the curve has one peak with a long tail to the left so is unimodal, left skewed. (The mode is the highest number of data points with the same value)
d. Distractor: The curve is clearly asymmetrical as the shape is not the same on each side of the highest number of data points.

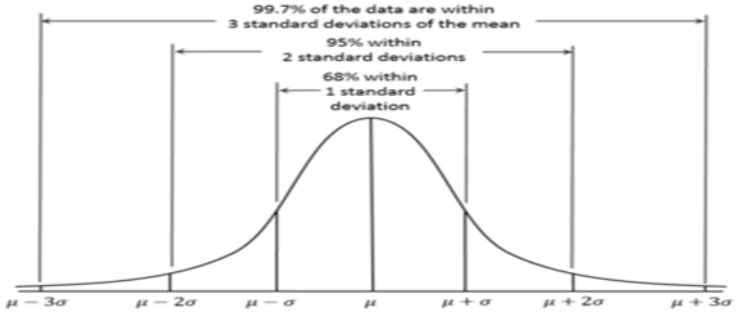
Question 3

Correct answer:

a. The mean may be 0 but can be any value so it is not necessarily a feature of the normal distribution curve.

Marking memorandum:

a. This is the correct answer. The mean may be zero but is not necessarily so. If the mean is zero the curve is known as the standard normal distribution
b. Distractor: If the distribution is normal then 68% of the data set falls within one standard deviation either side of the mean.
c. Distractor: If the distribution is normal then 95% of the data set falls within two standard deviations on either side of the mean.
d. Distractor: The normal distribution curve is always symmetrical.



Question 4

Correct answer:

b. Specificity is the ability of a test to correctly identify persons with(out) the disease (i.e. the true negative rate) B/B+C

Marking memorandum: (with reference to the table below)

a. Distractor: Sensitivity is the ability of a test to correctly identify persons with the disease i.e. detect the true positive rate A/A+C. This statement is therefore correct.
b. Correct answer: Incorrect statement so the correct answer to the question. A correct statement would be: Specificity is the ability of a test to correctly identify persons without the disease or B/B+C. The equation is correct.
c. Distractor: This is a correct statement. The Positive predictive value is the probability that subjects with a positive screening test truly have the disease or A/A+B
d. Distractor: This is a correct statement. The Negative predictive value is given by the value D/C+D. It is the probability that subjects with a negative screening test truly do not have the disease

		True class: Positive	True class: Negative	Measures
Predicted class	Positive	True positive *TP*	False positive *FP*	Positive predictive value (PPV) $\frac{TP}{TP+FP}$
Predicted class	Negative	False negative *FN*	True negative *TN*	Negative predictive value (NPV) $\frac{TN}{FN+TN}$
Measures		Sensitivity $\frac{TP}{TP+FN}$	Specificity $\frac{TN}{FP+TN}$	Accuracy $\frac{TP+TN}{TP+FP+FN+TN}$

Question 5

Correct answer:

a. the area labelled “a”

Marking memorandum:

a. Correct answer. The area labelled “a” represents the Type 1 or α error.
b. Distractor: The area labelled “b” represents a correct decision to accept H_o when H_o is in fact true.
c. Distractor: The area labelled “c” represents a correct decision to reject H_o when H_o is in fact false
d. Distractor: The area labelled “c” represents the type 2 or β error.

Truth table

	Reject	*Accept*
H_0 True	Type 1 or α error	Correct
H_0 False	Correct	Type 2 or β error

Question 6

Correct answer:

d. $10^0 = 10$ is not mathematically correct as any number raised to the power of 0 is equal to 1

Marking memorandum:

a. Distractor: This equation is correct since $e^0 = 1$
b. Distractor: This equation is correct since $2^6 = 64$ hence $\text{Log}_2 (64) = 6$
c. Distractor: This equation is correct since 1/8 =0.125 hence $\text{Log}_8 (0.125) = -1$
d. Correct answer as this statement is incorrect. $10^1 = 10$. Any number raised to the power of 0 equals 1

Question 7

Correct answer:

b. Graph B

Marking memorandum:

a. Distractor: Graph A is the graph of the linear function y = mx + 1 with a positive gradient.
b. Correct Answer. As x approaches 0 y approaches infinity and as x approaches infinity y approaches zero.
c. Distractor. Graph C is the graph of an exponential function e.g. $y = c^x$.
d. Distractor. Graph D is the graph of the linear function y= mx + c but with m negative i.e. negative gradient and c = 1.

Question 8

Correct answer:

c.

Question 9

Correct answer:

a.

Question 10

Correct answer:

d.

Question 11

Correct answer:

a.

Question 12

Correct answer:

c.

Question 13

Correct answer:

a.

Power analysis allows for the ability to detect a significant difference if one exists.

Question 14

Correct answer:

c.

Question 15

Correct answer:

c.

SBA SESSION SIX:
Peripheral nerve stimulation, Local Anaesthetics, Intermediary Metabolism

Question 1

Which is the least likely mechanism of action of intravenous lipid emulsion (ILE) therapy in the management of LAST?

a. Acting as a intravascular lipid sink that binds and inactivates lipophilic local anaesthetic molecules
b. Promotion of mitochondrial fatty acid metabolism and ATP synthesis in myocardial cells
c. Reversibly binding to and inactivating sodium channels
d. Direct inotropic effect due to increased intracellular myocardial content

Question 2

With regard to LAST the most common cardiovascular feature seen amongst reported cases is:

a. Hypertension
b. Hypotension
c. Tachycardia
d. Dysrhythmias

Question 3

Which of the following physicochemical properties most accurately refers to bupivacaine?

a. Molecular weight 234
b. pKa of 7.9
c. Plasma protein binding percent 90-97
d. Partition coefficient of 2.9

Question 4

Following profound neuromuscular block with an intermediate acting non-depolarising muscle relaxant, the time to the first detectable Train of Four (TOF) response after the appearance of post tetanic twitches will be:

a. 4.5 min
b. 8.5 min
c. 12.5 min
d. 16.5 min

Question 5

Which of the following is not a characteristic of an ideal peripheral nerve stimulator?

a. Square wave impulse
b. Delivered current 0 – 70 mA
c. Constant voltage
d. Stimulus duration of 0.2 – 0.3 ms

Question 6

Which of the following is incorrect? When compared to electrical nerve stimulation, magnetic nerve stimulation:

a. Is more painful
b. Cannot be used for Train of Four monitoring
c. Is difficult to achieve supramaximal stimuli
d. Equipment is bulky

Question 7

A 56 year-old woman is booked for a total colectomy for carcinoma of the colon. She undergoes general endotracheal anaesthesia with propofol, fentanyl and rocuronium and is maintained on 0.8 MAC isoflurane in an air/oxygen mixture. As she is allergic to penicillin, she receives clindamycin, gentamicin and metronidazole for surgical prophylaxis. At the end of the procedure, she is reversed with 2.5mg of neostigmine and 0.5mg of atropine. In the recovery unit, the patient appears restless and complains of double vision (diplopia). Her oxygen saturation is 99% on supplemental oxygen.

The drug most likely to be primarily responsible for her diplopia and restlessness is:

a. Atropine
b. Clindamycin
c. Gentamicin
d. Rocuronium

Question 8

A 19 year-old man undergoes a modified rapid-sequence induction using propofol, fentanyl and a 0.9 mg/kg dose of rocuronium for a laparoscopic appendicectomy. Maintenance is with Isoflurane in an air/oxygen mixture. The procedure ends after 50 minutes. Stimulation of the adductor pollicis with a peripheral nerve stimulator reveals a train-of-four (TOF) response of 4 with fade.

Which one of the following statements is true:

a. Fade may be explained by post-synaptic drug-receptor interactions
b. Tactile and visual detection of fade may be absent at TOF ratios above 0.4
c. Stimulation of facial muscles is an accurate reflection of the degree of block.
d. Extubation of a patient is recommended when the TOF ratio reaches at least 0.7

Question 9

A 42 year old man (weight 120kg, height 170 cm) is booked for an urgent repair of a corneo-scleral laceration after a work-related incident. After pre-oxygenation, he is induced with a total of 250 mg of Propofol, 150 µg of fentanyl and 120 mg of rocuronium. Cricoid pressure is applied by an assistant. Repeated attempts at intubation are unsuccessful, even after release of cricoid pressure. Mask ventilation is difficult and inadequate, exacerbated by the presence of a hard, plastic eye-protector. A decision is made to effect immediate reversal of neuromuscular block using sugammadex.

What dose of sugammadex is indicated in this instance?

a. 1920 mg
b. 720 mg
c. 480 mg
d. 240 mg

Question 10

Gastric emptying is slowed by:

a. high caloric fatty meals and the secretion of gastrin
b. local duodenal distension and increased parasympathetic tone
c. hormones such as cholecystokinin, secretin, and gastric inhibitory peptide (GIP)
d. parasympathetic postganglionic noradrenaline release

Question 11

Regarding neural control of intestinal motility:

a. The parasympathetic system decreases the activity of intestinal smooth muscle.
b. Sympathetic activity generally increases the activity of intestinal smooth muscle while contracting sphincters.
c. Meissners plexus is mainly involved in control of intestinal secretions. The myenteric plexus is mainly involved with motor control.
d. The intrinsic system cannot function autonomously because it requires interaction with the extrinsic component

Question 12

Regarding measurement of the cortical EEG signal used in processed EEG Depth of Anaesthesia monitors available:

a. Signal strength from cortical potential measured through the scalp is large enough that the voltage is required to be stepped down so that it becomes more measurable?
b. Three electrodes are required to triangulate the signal site?
c. Three electrodes are required to minimise the impact of electrical impedance when recording the cortical potentials?
d. The combined waveforms are subject to a Fourier analysis, and then individual frequencies used to plot a power spectrum

Question 13

In relation to the autonomic and limbic nervous systems in the brainstem:

a. The parasympathetic system originates in the dorsal vagus nucleus, and nucleus ambiguous, in the medulla. The efferent nerves from these centres largely form the vagus nerve.
b. The autonomic region of the medulla also has neuronal input from the pituitary, at the base of the brain
c. The reticular formation is thought to be part of the limbic system, responsible for higher functions such as emotions, and is of not considered a site of action for commonly used general anaesthetic agents.
d. The pontine tegmentum is responsible for initiating the early stages of Non-REM sleep

Question 14

The blood brain barrier is critical for the functioning of the brain and spinal cord, its structural contribution includes:

a. Tight junctions are formed by endothelial cells held together by Junctional Adhesion Molecules (JAM's) including the Claudin and Occludin families of proteins
b. Foot processes extending from surrounding astrocytes form the innermost layer
c. Endothelial cells form the layer outside the foot processes layer
d. Pericytes have a leukocyte lineage, and form a far more prominent layer around capillaries in the blood brain barrier than in capillaries in muscle beds

Question 15

A volatile anaesthetic agent has a saturated vapour pressure of 32kPa at room temperature. If the total fresh gas flow is 5L/min of which 500ml/min is directed through the vapourising chamber, Assuming the gas leaving the vaporising chamber is fully saturated with vapour, the resultant concentration of volatile reaching the patient will be:

a. 0.5%
b. 1.6%
c. 2%
d. 3.2%

Answers

Question 1

Correct answer

c. Reversibly binding to and inactivating sodium channels

Marking Memorandum

The mechanism of action of ILE therapy is poorly understood but a, b and d are all thought to play a role. c is the mechanism of action of local anaesthetics.

Question 2

Correct answer

d. dysrhythmias

Marking Memorandum

All may be seen but dysrhythmias were reported most commonly

Question 3

Correct answer

c. Plasma protein binding percent 90-97

Marking Memorandum

A, b and d refer to lignocaine. Bupivacaine is 288, 8.1 and 28 respectively.

Question 4

Correct answer

b. 8.5 minutes

Question 5

Correct answer

c. Constant voltage

Marking Memorandum

The current will vary as skin resistance changes.

Question 6

Correct answer

a. Is more painful

Question 7

Correct answer

d. Rocuronium

Marking Memorandum

In this instance, atropine was administered to counteract the muscarinic effects of neostigmine. Atropine given on its own causes blurred vision but not diplopia.
Clindamycin and gentamycin enhance the effect of NMBs but does not cause neuromuscular blockade.

The patient has residual block due to inadequate reversal of rocuronium whose effect has been enhanced by clindamycin, gentamicin and possibly residual isoflurane.

Question 8

Correct answer

b. Tactile and visual detection of fade may be absent at TOF ratios above 0.4

Marking Memorandum

Studies have shown that even experienced anaesthetists are not able to accurately detect fade when the TOF ratios are above 0.4.

NMBs produce twitch fade during repetitive stimulation by binding to the presynaptic acetylcholine (ACh) nicotinic receptors and inhibiting the positive auto-feedback action of ACh on its own release elicited during repetitive stimulation. This action of NMBs causes the stimuli following the first stimulus to release fewer ACh molecules resulting in a progressive decrease in twitch height in the TOF.

Facial muscles are much more resistant to muscle relaxants (hence overdosing possible) and are more prone to direct stimulation than the adductor pollicis muscle.

The currently accepted ratio for adequate recovery from neuromuscular block is the return of TOF ratio to greater or equal to 0.9.

Question 9

Correct answer

a. 1920 mg

Marking Memorandum

Recommended dose for immediate reversal of high-dose rocuronium in a CICV airway scenario is 16 mg/kg calculated to actual body weight.

Question 10

Correct answer

c. These hormones inhibit gastric emptying.

Marking Memorandum

a. Incorrect. Gastric emptying is slowed by gastric factors such as high caloric fatty meals. Gastrin, however, speeds up gastric emptying.
b. Incorrect. Duodenal factors such as local duodenal distension DO slow gastric emptying. However, increased *sympathetic* tone, rather than increased parasympathetic tone, slows emptying. Think of “fight or flight”
c. Correct.
d. Incorrect. Postganglionic parasympathetic fibres release acetylcholine to increase gastric emptying, whilst postganglionic sympathetic fibres release noradrenaline to decrease gastric emptying.

Question 11

Correct answer

c. Meissner’s plexus is mainly involved in control of intestinal secretions. The myenteric plexus is mainly involved with motor control.

Marking Memorandum

The gastrointestinal tract is regulated, partly, by the autonomic nervous system, which has an extrinsic and an intrinsic component. The extrinsic component is the sympathetic and parasympathetic innervation of the gastrointestinal tract. The intrinsic component is called the enteric nervous system, which consists of submucosal (Meissner) and myenteric (Auerbach) plexuses in the wall of the gastrointestinal tract. The parasympathetic system increases the activity of intestinal smooth muscle. Sympathetic activity generally decreases the activity of intestinal smooth muscle while contracting sphincters. The Intrinsic system can function autonomously.

Question 12

Correct answer:

d. The combined waveforms are subject to a Fourier analysis, and then individual frequencies used to plot a power spectrum

Marking memorandum:

a. Signal strength from cortical potential measured through the scalp an order of magnitude less than the cardiac potentials measured through the thorax on an ECG. EEG voltages 3 orders of magnitude less than ECG recording, A typical adult human EEG signal is about 10 µV to 100 µV in amplitude when measured from the scalp and an ECG is calibrated with 10 mV
b. There is no triangulation, the skull and scalp act as a diffuse filter, so measurements cannot be precise, and the EEG is a measurement of difference in potential between two points on the scalp.
c. Electrical resistance/impedance is a challenge, but is overcome by prepping the skin with alcohol wipes and a light abrasion and not by using extra electrodes.

Question 13

Correct answer:

a

Marking memorandum

a. The parasympathetic system originates in the dorsal vagus nucleus, and nucleus ambiguous, in the medulla. The efferent nerves from these centres largely form the vagus nerve
b. The autonomic region of the medulla also has neuronal input from the hypothalamus, and the hypothalamus is connected to the pituitary, but there are no neuronal connections between the medulla and the pituitary.
c. The reticular formation is part of what is called an 'activating system", and as such seems important for initiating sleep; and maybe anaesthesia. It may be an area where general anaesthesia is initiated or maintained
d. The pontine tegmentum is responsible REM sleep, and seems critical for initiating REM and the akinesia associated

Question 14

Correct answer

a.

Marking memorandum

a. Tight junctions are formed by endothelial cells held together by Junctional Adhesion Molecules (JAM's) including the Claudin and Occludin families of proteins.
b. Foot processes do originate from astrocytes but form the outermost layer.
c. Endothelial cells are the inner layer, closest to the blood.
d. Pericytes have vascular smooth muscle lineage, and do form a far more prominent layer around capillaries in the blood brain barrier (30-70% coverage) than in capillaries in muscle beds (1% coverage)

Question 15

Correct Answer

d. 3.2%

Marking Memorandum

Correct answer 3.2%: 10% of FGF goes through vaporising chamber. SVP 32 kPA. Dalton's law of PP. 10% of 32kPA is 3.2%.

SBA SESSION SEVEN:
Defence of intravascular volume, renal physiology, TEG

Question 1

Which of the following are considered early signs of shock?

a. Tachycardia
b. Confusion
c. Hyperlactataemia
d. Poor capillary refill
e. Cold extremities

Question 2

The following is true in terms of the monitoring of a hypovolaemic patient:

a. Stroke volume variation (SVV) exceeds 12%
b. Systemic vascular resistance is increased in compensation for the low stroke volume to preserve cardiac output
c. Blood pressure shows a widening of the pulse pressure
d. The diastolic pressure is a surrogate of the perfusion pressure.
e. The pulse contour analysis monitors can measure the stroke volume and assess fluid responsiveness.

Question 3

Passive leg raising is the tool used to assess fluid responsiveness. Which of the following statements are most correct?

a. Passive leg raising assesses the venous return to the right side of the heart
b. A positive response to passive leg raising requires a increase in the MAP by 10%
c. Physiologically, the passive leg raise increases the stroke volume
d. The passive leg raise test cannot be performed in awake patients
e. Passive leg raising is unhelpful in patients who have the IVC tied off.

Question 4

A 58 year old man with myeloma presents with a history of back pain. His biochemistry is as follows:

Sodium	130 mmol/l
Potassium	4.9 mmol/l
Creatinine	135 µmol/l (1.5 mg/dl)
Urea (BUN)	18 mmol/l (50 mg/dl)
Total protein	110 g/l
Albumin	30 g/l

What is the cause of his hyponatraemia?

a. Acute renal failure due to Bence Jones protein
b. Innapropriate secretion of ADH
c. Pseudohyponatraemia
d. Dilutional hyponatraemia due to fluid overload

Question 5

A 32 year old man with a base of skull fracture develops polyuria. His biochemistry is as follows:

Sodium	150 mmol/l
Potassium	4.1 mmol/l
Creatinine	95 µmol/l (1.1 mg/dl)
Urea (BUN)	12 mmol/l (34 mg/dl)
Serum osmolality	327 mOsm/l
Glucose	4.3 mmol/l (78 g/dL)

What is the likely diagnosis?

a. Dehydration due to osmotic diuresis
b. Diabetes insipidus due to traumatic brain injury
c. Seizure activity causing rhabdomyolysis and consequent acute kidney injury
d. Salt wasting syndrome due to traumatic brain injury

Question 6

A 73 year old patient presents with convulsions. He is clinically euvolaemic. His biochemistry is as follows:

Sodium	104 mmol/l
Potassium	4.1 mmol/l
Creatinine	114 µmol/l (1.28 mg/dl)
Urea (BUN)	15 mmol/l (42 mg/dl)
Serum osmolality	234 mOsm/l
Urine osmolality	245 mOsm/l
Urinary sodium	78 mmol/l

What is the likely cause for the hyponatraemia?

a. Cerebral salt losing state
b. Innapropriate ADH secretion
c. Hyponatraemia due to acute renal failure
d. Renal tubular acidosis

Question 7

A premature female infant born 2 days ago (gestational age 32 weeks, birth weight 1400g) has been booked for a central line placement due to difficult intravenous access. Her plasma creatinine level at birth was 75 umol/L. The creatinine level of 75 umol/L:

a. Is within normal limits in relation to the infant's size and muscle mass
b. May reflect maternal transfer of creatinine and reflect the mother's creatinine levels
c. May remain elevated for the first 6 months of the infant's life
d. Is related to a higher glomerular filtration rate (GFR) seen in neonates with lower gestational ages

Question 8

The 24-hour creatinine clearance is a widely used test for estimation of a patient's Glomerular Filtration Rate (GFR). Limitations of the 24-hour creatinine clearance include:

a. In a patient with normal renal function, the test underestimates the patient's true GFR
b. Creatinine is a poor marker of GFR, as a percentage is reabsorbed by the kidney
c. As the GFR falls, there is a greater overestimation of the GFR
d. 24-hour urine collection is unnecessary, as shorter collection times give comparable results

Question 9

A 32 year old female presents for an emergency caesarean section for fetal distress. Her s-creatinine level has been noted to have risen from 50 to 90 umol/L. The s-creatinine level of 90 umol/L in this patient:

a. Is within normal limits for a pregnant female
b. Is unlikely to reflect renal injury as there is only a small fluctuation in her creatinine levels
c. Is high, as s-creatinine levels are expected to decrease in pregnancy due to an increase in glomerular filtration rate.
d. Level would have been far more elevated if renal damage was secondary to pre-eclampsia

Question 10

The highest resorption of bicarbonate and ions occurs in the:

a. Proximal convoluted tubule
b. Loop of Henle
c. Distal tubule
d. Collecting tubule

Question 11

The following substances result in vasoconstriction:

a. Nitric oxide
b. Atrial Natriuretic peptide
c. Acetylcholine
d. Serotonin/bradykinin

Question 12

In the distal convoluted tubule, sodium reabsorption is regulated by:

a. Dopamine
b. Luminal sodium concentration
c. Angiotensin II
d. Noradrenaline

Question 13

The cortical and medullary collecting ducts have a low urea permeability, however the urea permeability can be increased under the influence of:

a. An increase in osmolality and ADH
b. A decrease in osmolality and ADH
c. A decrease in osmolality and an increase in ADH
d. An increase in osmolality and a decrease in ADH

Question 14

The juxtaglomerular apparatus consists of the following cell types:

a. Macula densa and Juxtaglomerular cells
b. Podocytes and mesangial cells
c. The macula densa, lacis cells (also known as extraglomeular mesangial cells) and juxtaglomerular cells
d. Principal cells (P cells) and Intercalated cells (I cells)

Question 15

Thromboelastography (TEG) assesses the visco-elastic properties of whole blood. Which of the following are most correct?

a. TEG is able to assess the functional activity of platelets
b. The TEG warms blood to 37^0C before the test commences
c. The integrity of clot formation can be assessed using the Clot index parameter
d. The TEG has the ability to assess global coagulation *in vitro*
e. The TEG has the ability to measure clot breakdown

Answers

Question 1

Correct answer

d. Poor capillary refill

Marking Memorandum

Tachycardia is non-specific
Confusion is a late sign
Rising lactate appears when lactate production outstrips clearance of lactate and indicates severe disease.
Cold extremities is a compensatory mechanism indicative of severe disease

Question 2

Correct answer

b. Systemic vascular resistance is increased in compensation for the low stroke volume to preserve cardiac output

Marking Memorandum

Physiologically, the SVR is always increased early to maintain cardiac output as the SV falls.

SVV is only validated if the patient is mechanically ventilated
The pulse pressure typically narrows in hypovolaemia
Diastolic blood is only used as a surrogate of coronary perfusion pressure.
The pulse contour analysis monitors derive SV using algorithms specific for each monitor.

Question 3

Correct answer

c. Physiologically, the passive leg raise increases the stroke volume

Marking Memorandum

The PLR increase SV significantly in patients who are fluid responsive.

The venous return is affected by many factors other than raising the legs of the patient
MAP should not be used to assess the response to a PLR
The PLR can be used in awake patients.
The PLR can be used in patients who have had the IVC tied off once collaterals have been formed via the azygos system

Question 4

Correct answer

c. Pseudohyponatraemia due to hypergammaglobulinaemia

Marking Memorandum

Acute renal failure is only likely if urinary electrolytes and osmolality is given
SIADH diagnosis requires the plasma osmolality and urinary osmolality to be stated. The diagnosis requires a low plasma osmolality in relation to normal urinary osmolality and normal urine sodium.
Dilutional hyponatraemia is only likely if the plasma albumin is also low.

Question 5

Correct answer

b. Diabetes insipidus due to traumatic brain injury

Marking Memorandum

Dehydration is unlikely since there is no features of increased osmotically active molecules e.g. glucose is normal

Not enough evidence for acute kidney injury due to rhabdomyolysis, and renal function shows a pre-renal picture
Cerebral salt wasting syndrome requires a urinary sodium which is usually elevated due to increased urinary losses.

Question 6

Correct answer

a. Cerebral salt losing state

Marking Memorandum
Cerebral salt losing state due to increased urinary sodium loss and the euvolaemic state.

Inappropriate ADH secretion requires a normal urine osmolality and relatively normal urinary sodium.
Hyponatraemia due to acute renal failure is possible but the patient would essentially be clinically fluid overloaded.
Renal tubular acidosis causes an elevation of serum sodium due to increased losses of free water an inability to acidify urine.

Question 7

Correct answer

b. May reflect maternal transfer of creatinine and reflect the mother's creatinine levels

Marking Memorandum
The plasma level is elevated in relation to the infant's size and muscle mass
Creatinine levels typically remain elevated for the first 1 to 2 weeks of life
Neonates with lower gestational ages have a lower GFR than term infants

Question 8

Correct answer

c. As the GFR falls, there is a greater overestimation of the GFR

Marking Memorandum
As the GFR falls, there is an associated decrease in creatinine filtration and excretion, resulting in an increase in serum creatinine that in turn stimulates increased creatinine secretion in the proximal tubule

Some creatinine is cleared from plasma through proximal tubular secretion. The test therefore overestimates the true GFR by 10-20%
Creatinine is freely filtered across the glomerulus, and is not reabsorbed or metabolized by the kidney
Creatinine excretion varies throughout the day. An incomplete urine collection will therefore lead to an underestimation of creatinine excretion.

Question 9

Correct answer

c. Is high, as s-creatinine levels are expected to decrease in pregnancy due to an increase in glomerular filtration rate.

Marking Memorandum
S-creatinine levels ↓ by an average of 35 umol/L to 35-70 umol/L (vs 49-90 in non-pregnant females).
Therefore renal injury may present with only small fluctuations in s-creatinine despite significant decline in renal function.
In a study conducted in pre-eclamptic patients, only a minority of patients had a s-creatinine level that exceeded non-pregnant levels, even in those with preeclampsia associated with ↓GFR of up to 40%

Question 10

Correct answer

a. Proximal convoluted tubule

Question 11

Correct answer

b. Atrial Natriuretic peptide

Question 12

Correct answer

b. Luminal sodium concentration

Marking Memorandum

Sodium reabsorption is regulated by the intraluminal concentration of sodium, and is not under the influence of neurohormones

Question 13

Correct answer

a. An increase in osmolality and ADH

Question 14

Correct answer

c. The macula densa, lacis cells (also known as extraglomerular mesangial cells) and juxtaglomerular cells

Marking Memorandum

Podocytes and mesangial cells are found in the glomerulus
Principal cells (P cells) and Intercalated cells (I cells) make up the epithelium of the collecting ducts

Question 15

Correct answer

d. The TEG looks at global coagulation *in vitro*

Marking Memorandum

The TEG analyses global *in vitro* coagulation: clot initiation, amplification, stabilization and breakdown of clot

The TEG cannot assess platelet function
The temperature can be set based on the body temperature
Clot integrity is measured using a derived parameter called the G-value which looks at the shear forces between pin and cup
Fibrinolysis is not measured but derived after 30min, looking at the lysis index

SBA SESSION EIGHT:
Volatile Kinetics, Endothelium, Inflammatory Cascade

Question 1

The LD_{50} for propofol in mice has been determined experimentally at 320mg/kg. Experimentally the LD_{50} is:

a. Determined in phase 1 clinical trials.
b. Determined from the log of the dose-response curve.
c. Determined as the mean dose of drug that kills half of the mice.
d. Determined as a measure of the acute toxicity of a drug.

Question 2

Regarding the elimination half-life of the intravenously administered hypnotic agent thiopentone:

a. The elimination half-life is dependent on the amount of thiopentone in the body.
b. The elimination half-life is independent of the clearance of thiopentone.
c. The volume of distribution of the drug influences its elimination half-life.
d. The elimination half-life is the most important determinant of emergence from anaesthesia after an induction dose.

Question 3

Regarding a target controlled infusion of propofol:

a. The Marsh model incorporates age into its calculations and is therefore the best model for use in the elderly.
b. When using the Marsh model, effect site targeting is less likely to cause haemodynamic embarrassment than plasma site targeting.
c. The Schnider model calculates ideal body mass for the patient and calculates doses and infusion rates accordingly.
d. Both the Marsh and Schnider models can be utilised in effect site targeting as even though they employ a different elimination constant (Ke0)

Question 4

Regarding the movement of gases and volatile inhalational agents in a circle system during low flow anaesthesia:

a. Lowe's formula estimates the uptake of oxygen from the circuit
b. Severinghaus' formula estimates the uptake of nitrous oxide from the circuit
c. Gay-Lussac's formula estimates the rate of denitrogenation of the circuit.
d. Formalin accumulation is responsible for prolonged emergence after low flow anaesthesia.

Question 5

During low-flow anaesthesia, CO_2 absorbents:

a. React exothermically with volatile anaesthetic agents.
b. May produce carbon monoxide when lithium hydroxide lime is used
c. May produce $CaCO_3$ as an insoluble precipitate.
d. May produce Compound A when exposed to high concentrations of enflurane.

Question 6

Regarding the physical properties of the inhalational anaesthetic agents:

a. Blood: gas partition co-efficient - Isoflurane > Sevoflurane > Desflurane > Xenon
b. Minimum alveolar concentration – N20 > Methoxyflurane > isoflurane > Halothane
c. Percent metabolized by the patient - Halothane > Enflurane > Sevoflurane > Desflurane
d. Saturated vapor pressure at 20 C - Desflurane > Sevoflurane > Isoflurane > Halothane

Question 7

Regarding the concomitant use of two different inhalational anaesthetic agents:

a. The effect of administering two inhalational agents is synergistic in reducing minimum alveolar concentration.
b. Xenon has a lower blood: gas partition coefficient than nitrous oxide and a second gas effect is not expected to take place if used with a volatile agent.
c. The concentration effect is the increase in the rate that the Fa/Fi ratio rises as the alveolar concentration of that gas is increased.
d. Methoxyflurane, due to its high blood: gas partition co-efficient would exert a concentration effect on co-administered desflurane.

Question 8

Regarding the metabolism of inhalational agents:

a. Sevoflurane is metabolised in the liver to form hexafluoroisopropanol, Compound A and Compound B.
b. In contrast to rats, humans have high levels of renal cysteine conjugate β-lyase enzymes which protects them from Compound A toxicity.
c. The risk of hepatitis after exposure to a volatile agent correlates to the degree to which these agents undergo oxidative phosphorlation.
d. Desflurane, halothane, and isoflurane all not metabolized to trifluoroacetate, which makes them less likely to cause hepatotoxicity through an immunologic mechanism.

Note: THE FOLLOWING VIGNETTE REFERS TO QUESTIONS 9, 10 & 11 THAT FOLLOW:
A well patient develops severe cardiovascular collapse and evidence of bronchospasm, five minutes after intravenous induction of general anaesthesia with fentanyl, propofol and rocuronium. His anaesthetist diagnoses anaphylactic shock.

Question 9

An anaphylactic reaction is:
a. a predictable adverse drug reaction.
b. a Type 1 hypersensitivity reaction.
c. mainly involves the production of IgG antibodies.
d. is an allergic reaction

Question 10

This anaphylactic reaction was most probably caused by:
a. Fentanyl
b. Latex products
c. Propofol
d. Rocuronium

Question 11

The immediate management of anaphylactic shock entails:

a. Undiluted adrenaline 0.5-1mg given intravenously.
b. Decreasing volatile concentration and providing 100% oxygen.
c. Hydrocortisone 200mg intravenously.
d. Salbutamol nebulisations.

Note: THE FOLLOWING VIGNETTE REFERS TO QUESTIONS 12, 13 & 14 THAT FOLLOW:
A 25 year old otherwise healthy patient is booked for a washout and debridement of a septic leg wound. On examination the surrounding area is red and the patient has a temperature of 38 degrees Celsius.
The immune system is made up of an innate and adaptive system. The innate system has external and internal components.

Question 12

Which of the following forms part of the EXTERNAL components:

a. Acute Phase Proteins
b. Complement System
c. Mucosal Barriers
d. Proteolytic enzymes

Question 13

Which of the following forms part of the HUMORAL response:

a. B-lymphocytes
b. Leukocytes
c. Mast cells
d. Natural killer cells

Question 14

Local inflammation can lead to a systemic response, SIRS. Internal defences will simultaneously activate a compensatory anti-inflammatory response syndrome (CARS).
Which of the following components is not part of the CARS response?

a. IL 4
b. IL 6
c. IL 10
d. IL 13

Question 15

A 40-year-old patient known with a connective tissue disorder is booked for an explorative abdominal procedure. The patient is on chronic immunosuppressants, including systemic steroids.

Which of the following is an equivalent dose to 20mg oral Prednisone:

a. Cortisone 50mg
b. Dexamethasone 2mg
c. Methylprednisolone 6mg
d. Prednisolone 10mg

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ANSWERS

Question 1

Correct answer

d.

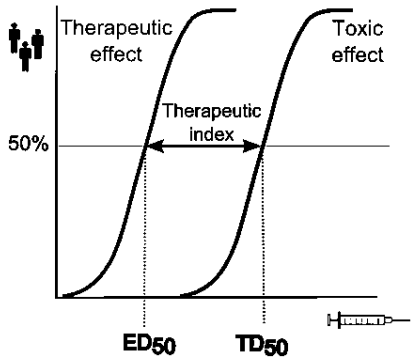
Marking memorandum

a. Incorrect, phase I clinical studies assess the safety of a drug or device in humans. This initial phase of testing usually involves a small number of healthy human volunteers, who are paid for participating in the study. The study is designed to determine the effects of the drug or device on humans including how it is absorbed, metabolized, and excreted. This phase also investigates the side effects that occur as dosage levels are increased

b. Incorrect, the dose response curve is a curve plotting the relationship between the dose of a drug administered and its pharmacological effect. It has no bearing on the lethal dose of the drug unless the effect of the drug would be to euthanase.

c. Incorrect as the LD50 refers to the median lethal dose not the mean lethal dose.
The median is the middle point of a number set, in which half the numbers are above the median and half are below.
The mean is the sum of all the numbers in the set divided by the amount of numbers in the set

d. Correct; the LD50 is a measure of acute toxicity of propofol



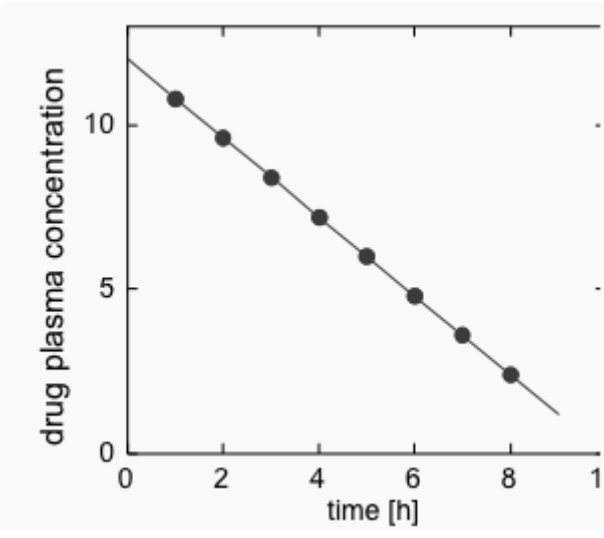
Question 2

Correct answer

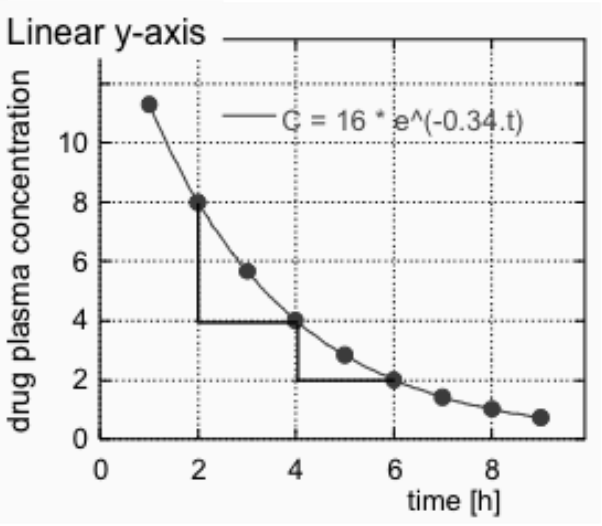
c.

Marking memorandum

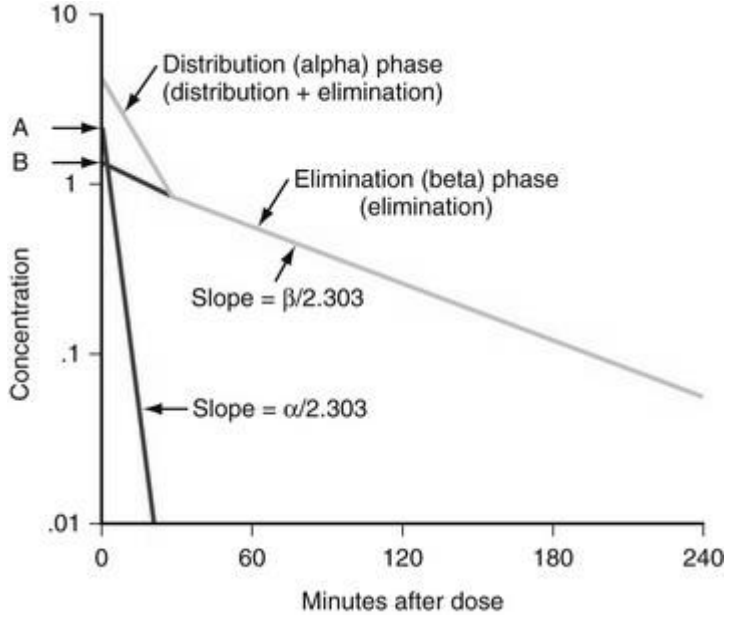
Zero-order kinetics



First-order kinetics



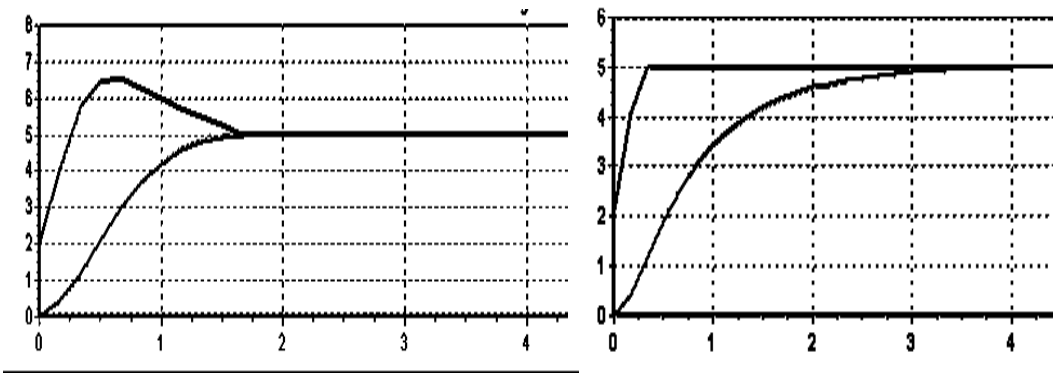
a. *Incorrect*. Thiopentone, like most other drugs we use, follows first order kinetics. The elimination half-life is independent of the amount of drug in the body. For first order elimination, the plasma concentration – time profile during the elimination phase shows an exponential decrease in the plot with linear axes. For example, 1% of the drug quantity is eliminated per minute. During zero order elimination kinetics the time profile during the elimination phase is linear and a fixed amount of drug is eliminated per unit time. Zero 0 elimination is rather rare, mostly occurring when the elimination system is saturated. An example is the elimination of Ethanol.
b. *Incorrect*. Half-life is intimately related to clearance as clearance is the sum of drug redistribution and elimination ($t_{½} = 0.693 \times Vd / CL$). Clearance can be defined as the amount of plasma completely cleared of a drug per unit time.
c. **Correct**. It is a key parameter as it is a primary determinant (together with clearance) of drug half-life. $t_{½} = 0.693 \times Vd / CL$. The distribution of the drug between the plasma and the tissues is at an equilibrium, when the elimination phase is reached.
d. *Incorrect*. The distribution half-life and not the elimination half-life is primarily responsible for emergence from anaesthesia after an induction dose.



Question 3

Correct answer: d

a. Incorrect. The Marsh model is only dependent on weight and does not take age into account. Other models (Schnider and Eleveld) that incorporate age into their algorithms would be more suitable in the elderly who have a lower lean body mass and would require lesser doses of propofol for induction and maintenance of a constant plasma concentration.
b. Incorrect. Effect site targeting achieves a rapid brain concentration at the expense of plasma propofol concentration and is therefore associated with more haemodynamic perturbance.



c. Incorrect. Schnider model uses weight, length and sex to calculate lean body weight (not ideal body weight) and is a good model to use in the elderly.Lean body weight is the difference between total body weight and fat mass.Ideal body weight is the ideal weight associated with maximum life-expectancy for a given height.

d. Correct. The Marsh and Schnider models can both be utilised in effect site targeting, but each model needs an algorithm specific Ke0.

Question 4

Correct answer b

Marking memorandum

a. Incorrect, Lowe's formula estimates the uptake of volatile agent from a circle system
$V_{AN} = f \times MAC \times \lambda_{B/G} \times Q \times t^{-½}$,
Where f is the desired anaesthetic concentration as a fraction of MAC, MAC is minimum alveolar concentration, $\lambda_{B/G}$ is the blood / gas solubility co-efficient, Q is the cardiac output and t is time. The uptake of oxygen can be estimated using the Brody formula for oxygen$VO2 = 10 \times [kg]^{¾}$

b. Correct, the instantaneous uptake of nitrous oxide at any given time for an adult patient of average weight can be roughly estimated using Severinghaus' formula
$V_{N20} = 1000 \times t^{-½}$ in ml/min.

c. Incorrect; formula doesn't exist, Gay-Lussac's law however, states that, for a given mass and constant volume of an ideal gas, the pressure exerted on the sides of its container is directly proportional to its absolute temperature.

d. Incorrect; formalin doesn't accumulate in the circuit. Acetone, argon, methane and ethanol may accumulate as unwanted trace gasses.

Question 5

Correct answer c.

Marking memorandum

a. Incorrect no exothermic reactions take place with the volatile agents. Reactions such as Compound A production with sevoflurane and carbon monoxide with desflurane, enflurane and isoflurane may however take place.

b. Incorrect. Lithium hydroxide lime (Litholyme) does not produce carbon monoxide from breakdown volatile agents under any circumstances, even when it is desiccated. Carbon monoxide may be produced by reactions with soda lime and volatile agents (desflurane > enflurane > isoflurane) >> (halothane = sevoflurane). Worse in dry absorbent. Turn oxygen off at end of case, change absorbent regularly, change if FGF left on over the weekend or overnight, and use low flows to keep granules moist.

c. Correct
$CO2\ (g) \rightarrow CO2\ (aq)$ (CO2 dissolves in water - slow and rate-determining)
$CO2\ (aq) + NaOH \rightarrow NaHCO3$ (bicarbonate formation at high pH)
$NaHCO3 + Ca(OH)2 \rightarrow CaCO3 + H2O + NaOH$

d. Incorrect, Sevoflurane is unstable in soda lime, producing Compound A (lethal at 130-340 ppm, or renal injury at 25-50 ppm in rats; but incidence of toxic [hepatic or renal] or lethal effects in millions of humans are comparable to desflurane). Compound A concentrations of 25-50 ppm are easily achievable in normal clinical practice. Sevoflurane package insert recommends avoiding FGF at 1 L/min for no more than 2 MAC-Hours

Question 6

Correct answer

a

Marking memorandum

a. Correct

b, c, d. Incorrect; see table below

	Isoflurane	Sevoflurane	Desflurane	Enflurane	Halothane	Methoxyflurane	N2O	Xenon
Blood:gas partition co-efficient	1.4	0.68	0.4	1.9	2.5	12	0.47	0.12
MAC	1.15	2.0	6.0	1.68	0.75	0.16	104	71
% Metabolised	0.2	5	0.02	2.4	20	70	0	0
SVP 20 C kPa	33	20.9	89.2	22.9	32	2.99	-	-

Question 7

Correct answer c

Marking memorandum

a. Wrong. The administration of two different inhalational agents would have an additive effect not synergistic. Synergy the joint action of agents, as drugs, that when taken together increase each other's effectiveness and the final effect is greater than the sum of the two effects.
b. Incorrect. As Xenon has a MAC of 71 it needs to be given in high concentration - a second gas effect, concentration effect and diffusion hypoxia effect could be anticipated.
c. Correct or otherwise put - The higher the concentration of an inhaled anaesthetic, the faster the alveolar concentration approaches the inhaled concentration. This is referred to as concentration effect and is clinically significant only in cases where gases are administered in high concentration.
d. Incorrect Methoxyflurane due to its low saturated vapor pressure cannot be given in high concentrations and cannot therefore exert a second gas effect.

Question 8

Correct answer c

Marking memorandum

a. Incorrect. Approximately 3% of the absorbed dose of sevoflurane is metabolised. It undergoes hepatic metabolism by cytochrome P450 (isoform 2E1). Hexafluoroisopropanol and inorganic fluoride are produced. The interaction of sevoflurane with carbon dioxide absorbents leads to the formation of several decomposition products. Compounds A, B, C, D and E have all been identified, although only compounds A and B (the latter being less toxic) are present in sufficient quantities to make analysis feasible.
b. Incorrect. Rodent experiments showed that when levels of Compound A reach 25–50 ppm or greater renal injury occurs. Human studies suggest a higher threshold for toxicity, explained by 20- to 30-fold lower levels of renal cysteine conjugate β-lyase enzymes, which converts Compound A into a reactive metabolite toxic to renal proteins. Total exposure expressed as the product of concentration by time correlates with injury. Human renal toxicity appears at ~150–300 ppm h. Prolonged exposure to sevoflurane, using a rebreathing system with a carbon dioxide absorber in lime, and low flows has been associated with transient biomarker evidence for renal injury, although urea and creatinine are unaffected. Significant clinical renal toxicity has not been associated with sevoflurane.
c. Correct. The National Halothane Study estimated the risk of fatal hepatic necrosis at one in 10 000 anaesthetics. Adult females are more commonly affected. Repeated exposure increases the risk of hepatitis. Less commonly hepatitis has been described after exposure to enflurane>isoflurane>desflurane and the risk of hepatitis correlates to the degree to which volatile agents undergo oxidative phosphorylation. Sevoflurane is not metabolized to antigenic

TFA–protein complexes. Although there have been a few case reports of postoperative sevoflurane hepatic toxicity, the association is very weak.

d. Incorrect. Desflurane, halothane, and isoflurane all are metabolized to trifluoroacetate, which can cause hepatotoxicity through an immunologic mechanism involving trifluoroacetyl hapten formation and an autoimmune response. The metabolite is trifluoroacetic acid (TFA), which is protein-bound and this TFA–protein complex can induce a T-cell-mediated immune response resulting in hepatitis ranging from mild transaminitis to fulminant hepatic necrosis and possibly death.

Question 9

Correct Answer

b.

Marking memorandum

a. Anaphylaxis is not a predictable side effect to a drug, but an unpredictable allergic or non-allergic reaction to a specific drug.
b. Anaphylaxis is categorised as a Type 1 hypersensitivity reaction.
c. Antigen exposure usually cause IgE antibody production. It is less often associated with IgG production.
d. Anaphylaxis can be an allergic or non-allergic reactions.

Question 10

Correct Answer

d.

Marking memorandum

a. Anaphylactic reactions are very rarely caused by synthetic opioids. Allergic reactions are sometimes seen with the use of morphine, codeine and meperidine due to histamine release induced by the tertiary amine structure.
b. Latex causes about 20% of perioperative anaphylactic reactions and this usually occurs up to 30-60 minutes post induction.
c. Incidence of anaphylactic reactions with Propofol and Thiopental are rare (1.2 – 2 %)
d. Correct answer. 60-70% of anaesthesia related anaphylactic reactions are caused by neuromuscular blocking agents

Question 11

Correct answer

b.

Marking memorandum

a. Adrenaline is part of the emergency immediate management of anaphylactic shock, but titrated doses of 50-100ug are given intravenously in this situation.
b. Emergency airway management in any emergency entails providing 100% oxygen. The volatiles are continued at a low concentration to minimise the worsening of the vasodilatory effects.
c. Systemic steroids are part of the subsequent management of anaphylactic shock.
d. Salbutamol nebulisations are part of the subsequent management of anaphylactic shock if bronchospasm persists.

Question 12

Correct Answer

c.

Marking memorandum

a. Acute Phase Proteins form part of the internal components, along with leukocytes, NK cells…
b. Complement system forms part of the internal components, along with Acute Phase Proteins, leukocytes, NK cells
c. Mucosal Barriers form part of the external components, along with skin, sweat, hairs/cilia…..
d. Proteolytic enzymes form part of the internal components, along with Acute Phase Proteins, Complement System, Leukocytes, NK cells….

Question 13

Correct Answer **a.** B-lymphocytes forms part of the humoral response

Marking Memorandum

a. B-lymphocytes form part of the humoral response with an antibody response mediated from the B-lymphocytes in the bone marrow
b. Leukocytes form part of the cell mediated response, circulating throughout the body in search of pathogens.
c. Mast cells form part of the cell mediated response. They react to pathogens and release a variety of mediators, eg histamine.
d. Natural killer cells form part of the cell mediated response. They are cytotoxic lymphocytes .

Question 14

Correct Answer b. IL 6 is a major component of SIRS

Marking Memorandum

a. IL 6 is a major component of SIRS, along with TNFalpha, IL1/6/8
b. IL 4 is a major component of CARS, along with IL10/11/13, LPS binding proteins…
c. IL 10 is a major component of CARS
d. IL 13 is a major component of CARS

Question 15

Correct answer b

Marking Memorandum

a. 5 mg systemic Prednisone is equal to 25mg Cortisone
b. 5mg systemic Prednisone is equal to 0,5-0.75mg Dexamethasone
c. 5mg systemic Prednisone is equal to 4mg Methylprednisolone
d. 5mg systemic Prednisone is equal to 5mg Prednisolone

SBA SESSION NINE

Question 1

You anaesthetise a 2kg 3 month old child for a ventriculoperitoneal shunt. Less than 10 minutes after induction of anaesthesia, prior to surgical prepping and infiltration of local anaesthesia, you notice that her temperature has dropped to 35.3^{o}C. This rapid drop in core temperature is unlikely to have been influenced by:

a. Vasoconstriction reducing peripheral perfusion
b. Patients initial heat content
c. Neonates and infants have a larger core compartment than adults
d. Body morphology

Question 2

With regard to gas cylinder Nitrous Oxide supply attached to the anaesthetic machine:

a. The cylinder was originally filled with nitrous oxide to a filling ratio of 0.85
b. The pressure in cylinder when newly attached to anaesthetic machine will be the saturated vapour pressure of nitrous oxide in the cylinder
c. The pressure in the cylinder will always read 44bar
d. The volume of the contents of the cylinder at 21 C will always remain at a constant vapour /liquid ratio

Question 3

The most serious consequence of inspiration of dry and cold gases via an endotracheal tube over a prolonged period of time is:

a. The moisture deficit that is incurred
b. Heat loss due to massic enthalpy of evaporation
c. Damage to the mucociliary escalator
d. Movement of the isothermic saturation boundary to a more distal level in the tracheobronchial tree.

Question 4

The following will reduce the airway response to intubation:

a. Propofol
b. β-blockers
c. Magnesium sulphate
d. Dexmedetomidine

Question 5

With reference to packed red cells:

a. Hyperglycaemia may occur as a direct result of the transfusion of several units of fresh packed red cells in an adult patient.
b. The addition of sodium citrate at donation reduces haemolysis of stored red cells
c. Packed red cells should not be transfused if over 28 days old
d. Washed packed red cells are prepared on donation and kept for patients with a history of severe recurrent allergic transfusion reactions.

Question 6

A prominent difference of Midazolam, compared to Dexmedetomidine is:

a. Faster awakening
b. Lack of respiratory depression
c. Anterograde amnesia
d. Opioid sparing effect

Question 7

The Number Needed to Treat (NNT) for 50% relief of pain in people with fibromyalgia is 22 for pregabalin compared with 3.6 for amitriptyline. This means that:

a. Amitriptyline is more appropriate for treating fibromyalgia than pregabalin.
b. Pregabalin is more appropriate for treating fibromyalgia than amitriptyline
c. Neither drug is particularly appropriate as a 50% pain relief is not clinically relevant
d. There is 22 fold risk of harm if people with fibromyalgia are treated with pregabalin

Question 8

In recent years, the incidence of HIV infection has fallen, however with the roll-out of ARVs, the prevalence rate has increased. This means that:

a. The number of people living with HIV in South Africa has increased.
b. The number of people living with HIV in South has decreased.
c. The number of people becoming infected with HIV is increasing.
d. The survival rate for people living with HIV is getting worse

Question 9

Patient Z is treated with clopidogrel for a drug eluting cardiac stent. Despite compliance with his medication he suffers an arterial thrombotic event. A possible reason for this could be:

a. He is on another drug that is an inhibitor of CYP2C19
b. He is on another drug that is an inducer of CYP 2C19
c. He has a genetic polymorphism of CYP2D6
d. He is an ultra-rapid metabolizer of clopidogrel

Question 10

A 30-year-old woman is training for her second Ironman. After 3 hours of training on her indoor bike at a heart rate of 145 bpm (submaximal exercise level), she sprints the last 500 m.

The Anaerobic Thereshold (AT) is defined as the point where oxygen-independent metabolism is required in addition to aerobic metabolism to sustain exercise performance. The physiological changes which take place as she reaches her AT are NOT characterized by:

a. Decreased $HCO3^-$
b. Oxyhaemoglobin dissociation curve shift to the left
c. Haemoconcentration
d. Increased plasma sodium concentration

Question 11

A 30-year-old woman is training for her second Ironman. She decides to add high intensity intervals to a 3-hour long training session. During these bursts of high intensity intervals, the physiological changes are characterized by:

a. Fall in pH due to increased lactic acid generation.
b. Increase in blood flow to muscle of 500-1000 ml per 100 g muscle per min.
c. Increase in oxygen consumption up to 20 times above resting oxygen consumption.
d. Increased ventilatory drive due to changes in arterial concentrations of oxygen and carbon dioxide.

Question 12

A 28 year old ASA 2 patient is anaesthetised for laser airway surgery. What is the safest combination of oxidizers?

a. FiO_2 0.3 with FiN_2O 0.7
b. FiO_2 0.3 with 70% helium
c. FiO_2 0.4 in Air
d. FiO_2 0.3 and EtO_2 0.6

Question 13

A clinical application of latent heat of vaporisation is seen when ethyl chloride is sprayed on to the skin and the skin cools rapidly. Latent heat of vaporisation:

a. Decreases as ambient temperature increases
b. Is the energy required to convert a solid to a liquid at a constant temperature
c. Is infinite at the critical temperature
d. Is the amount of heat required to raise the temperature of a given object by 1 Kelvin.

Question 14

MRI is not a suitable investigation to detect calcification in tumours and changes in cortical bone. The reason for this is that:

a. calcium does not emit a MRI signal
b. bone causes an acoustic shadow in the MRI signal
c. bone does not contain pulsatile elements
d. bone prevents penetration of the radiofrequency signal

Question 15

A 59-year-old patient receives liposomal morphine via the epidural route as part of their postoperative pain management for a hip replacement. She previously had metastatic breast cancer which was successfully treated with a combination of drugs which included liposomal doxorubicin. Liposomal drug delivery systems offer several advantages over traditional formulations because:

a. They form polymeric micelles which rapidly fuse with cell membranes
b. They are rapidly cleared by the reticuloendothelial cell network
c. They easily and preferentially encapsulate hydrophilic molecules
d. They can be altered with several ligands to target specific cells

Answers

Question 1

Correct Answer

a. Vasoconstriction reducing peripheral perfusion

Marking Memorandum

Vasodilation causes redistribution of heat from the core to the periphery. Redistribution accounts for the largest drop in core temperature.

More heat will be transferred from the warm core to a cold peripheral compartment and patients with cool peripheries will suffer a greater degree of core hypothermia.
Neonates and infants have a larger core compartment than adults. In neonates and infants, the core extends almost to the body surface and they have a very small peripheral compartment. This causes an accelerated heat loss because of an increased temperature gradient between the skin surface and the environment.
Obese patients tend to have warmer peripheries as the adipose tissue acts as a thermal insulator resulting in vasodilatation.

Question 2

Correct answer

b. The pressure in cylinder when newly attached to anaesthetic machine will be the saturated vapour pressure of nitrous oxide in the cylinder

Marking Memorandum

The pressure in the cylinder will vary with the saturation vapour pressure of the nitrous oxide , which in turn will depend on the temperature of the nitrous oxide, which in turn depends on ambient room temperature and ongoing flow of gas from cylinder which drops the temperature of the cylinder contents due to loss of heat to vaporisation.

The filling ratio (mass of nitrous oxide in cylinder/mass of water cylinder could hold) is usually 0.67 (0.85 is overfull and dangerous) Cylinders are filled by weight.
The pressure depends on the saturated vapour pressure of nitrous oxide, which is dependent on temperature of cylinder contents.
As the contents of the cylinder are used up the gas volume will increase and the liquid volume will decrease.

Question 3

Correct answer

c. Damage to the mucociliary escalator

Marking Memorandum

When the mucuos layer in the tracheobroncho tree becomes more viscous, the hyper-viscous layer may cause obstruction of bronchi, resulting in increased airway resistance, atelectasis, increased propensity to infection, greater V/Q mismatch. Ultimately cilia may disappear and the tracheal epithelium undergoes keratinization, ulceration and necrosis.

Total water losses in an adult are about 250 ml/ day and therefore easily correctable.
This amounts to about only about 20% of heat loss by the body. Heat loss due to massic enthalpy (latent heat of evaporation) usually occurs in the nose. With tracheal intubation the heating and warming occurs in the trachea which is not as well equipped to deal with cold dry gasses. Heat loss would be the same in both areas.
The isothermic saturation boundary is the level in the airways where gasses reach BTPS (body temperature and saturated vapour pressure with an absolute humidity of 44gm/cubic meter). This is usually in the proximal trachea.

Question 4

Correct answer

a. Propofol

Marking Memorandum

Propofol (2-3mg/kg) acts centrally to inhibit the sympathetic nervous system and dampens the baroreflex regulation mechanism. It also reduces pharyngeal reflexes and the cough reflex. It is more effective than the other induction agents at reducing the airway response to laryngoscopy and intubation.

β-blockers are effective at obtunding the cardiovascular response to laryngoscopy and intubation but have no effect on the respiratory or airway response. Esmolol (1-2mg/kg) is effective for hypertensive patients treated on β-blockers as well as normotensive patients. Labetalol (0.25-1mg/kg) although in higher doses this selective α_1 non-selective β-receptor antagonist will blunt the hypertensive response to intubation but tend to cause bradycardia so an intermediate dose (0.4mg/kg) is recommended. Several studies have found that pre-medication with oral β-blockers will reduce the incidence of hypertension and dysrhythmias on laryngoscopy and intubation but these appear less effective than intravenous medication.

Magnesium (20-40µg/kg) causes arterial dilation through α-antagonism with preservation of venous tone, calcium channel blockade resulting in (amongst other things) inhibition of adrenal catecholamine release and β-agonism. It is also a direct coronary vasodilator. Higher doses have been associated with hypotension and 30µg/kg appears to be the optimal dose. Rapid injection may cause an unpleasant flushing sensation for the patient. Although it has bronchodilator properties is not useful for blunting these or other airway responses to laryngoscopy and intubation.

Dexmedetomidine is a highly specific α_2-agonist which acts centrally to reduce sympathetic outflow and peripherally to reduce noradrenaline mediated vasoconstriction. Its sedating effects are due to presynaptic inhibition of the noradrenergic neurons in the locus ceruleus. If it is just for blunting of the intubation response a continuous infusion is unnecessary, a bolus of 0.7 - 1µg/kg over 10 minutes may be given. It does not directly reduce airway reflexes in response to intubation.

Question 5

Correct answer

a. Hyperglycemia may occur as a direct result of the transfusion of several units of fresh packed red cells in an adult patient.

Marking Memorandum

Dextrose is added to the storage bag as fuel for the cells during storage. At day 1 it is present at 24mmol/L, this reduces to 5mmol/L by 35 days. The possibility of hyperglycemia from blood transfusion must be considered were large volumes of fresh red cells relative to body size are given (e.g. Liver transplant or neonatal cardiac surgery)

Sodium citrate is present as an anticoagulant in the bag used for storing packed cells and whole blood. Saline and mannitol are the additives used to reduce haemolysis of red cells. Despite the addition of these two substances one can expect around 30% of red cells to be haemolysed by day 35.

Packed red cells can be stored for up to 42 days at 1-6 ^{0} C

Washed Red Cells are prepared on demand from banked packed cells. Cells are suspended in isotonic saline, centrifuged, saline removed and then re-suspended in isotonic saline for transfusion. They should be administered within 24 hrs because of the increased likelihood of bacterial contamination in preparation and the lack of nutrient admixture.

Washed cells are indicated in the following circumstances:

- Severe, recurrent allergic transfusion reactions
- Known IgA deficiency in patients who have formed anti-IgA antibodies

- Stored red cells which have been gamma irradiated (washes off the potassium which collects following irradiation, best managed by transfusing as soon as possible after irradiation)

Question 6

Correct answer

c. Benzodiazepines are unique in their ability to cause anterograde amnesia. This could be advantages where hospital procedure or admission is deemed traumatic but can also be a drawback in longterm sedation such as ICU admission when longer loss of memory is unsettling for patients.

Marking memorandum

a. Awakening after single equipotent sedation doses of Dexmedetomidine and Midazolam is quite similar with Dexmedetomidine causing less of a hangover effect.

b. Benzodiazepines cause slight respiratory depression that is exaggerated when combined with other sedatives especially opioids. Benzodiazepines and opioids display synergism with regards to sedation and respiratory depression. It also causes decreased muscle tone that can lead to airway obstruction in the obtunded patient.

c. Correct answer.

d. Benzodiazepines do not have any analgesic properties. Alpha 2 agonists have analgesic effects and decrease opioid requirements.

Question 7

Correct Answer

a. Amitriptyline is more appropriate for treating fibromyalgia than pregabalin.

Marking Memorandum

The Number Needed to Treat (NNT) is the reciprocal of the absolute risk reduction (1/ARR) and is often quoted to reflect the benefit of a drug. The NNT is often referred to as the number of patients which need to be treated to prevent a bad outcome (e.g. postoperative MI), in this example, it is being used to demonstrate the number of patients who need to be treated in order for one to achieve the favourable outcome (a clinically meaningful improvement of pain – which is a 50% reduction in pain). The NNT for pregabalin in fibromyalgia indicates that 22 people would need to be treated with the drug for one to get 50% pain relief while for amitryptilyne it is only 3.6 people.

Question 8

Correct Answer

a. The number of people living with HIV in South Africa has increased.

Marking Memorandum

Incidence is defined as the rate of new or newly diagnosed infections – so in this example the number of people acquiring the virus may be reducing. However, if the ARV rollout means that people are now living for longer, the prevalence (percentage of the population affected by the disease at a given time) may still increase because the death rate is reduced.

Question 9

Correct Answer

a. He is on another drug that is an inhibitor of CYP2C19

Marking Memorandum

Clopidogrel is a prodrug. If having MI then insufficient active metabolite formed so must be an inhibitor of CYP enzyme2C19

An inducer of CYP2C19 would result in increased active metabolite of clopidogrel as it is a prodrug and would result potentially in bleeding.
He may have a polymorphism of 2D6 but clopidogrel is not metabolized by 2D6
If he were an ultra-rapid metabolizer it would be the same as taking an inducer of CYP2c19, resulting in excess active drug and bleeding.

Question 10

Correct answer

b. Oxyhaemoglobin dissociation curve shift to the left

Marking Memorandum

The increase in the H^+ in the muscle capillary bed caused by the lactic acidosis facilitates the dissociation of oxygen from haemoglobin allowing for increased oxygen extraction – that is a RIGHT shift and not a LEFT shift in the oxyhaemoglobin dissociation curve.

$HCO3^-$ is reduced as it buffers lactate acidosis to maintain H^+ homeostasis.
The increased intra cellular lactate concentration promotes flux of extracellular fluid to balance the increased intracellular osmolality which results in haemoconcentration. This increase in red cell concentration increases O2 concentration providing more O2 per ml of blood flow.
During strenuous exercise, extracellular water volume is decreased as it shifts to the intracellular muscle space to balance the altered osmotic forces associated with increased lactate production, causing increased plasma sodium concentration.

Question 11

Correct Answer

c. Increase in oxygen consumption up to 20 times above resting oxygen consumption.

Marking Memorandum

The pH remains nearly normal even during high intensity training due to the buffer capacity of $HCO3^-$.
Blood flow to muscles at rest is usually 2-4 ml/100 g muscle/min. During maximal exercise this increases to about 100 ml/100 g muscle/min.
How respiration is stimulated during exercise is not completely understood. It is thought to be a combination of motor centre activity, afferent signalling from proprioceptors in muscles and joints as well as alterations in the sensitivity of chemoreceptors to PO_2 and PCO_2. The changes in PaO_2 and $PaCO_2$ are insufficient to account for the large increase in respiration.

Question 12

Correct Answer:

b. FiO_2 0.3 with 70% helium

Marking Memorandum

The ASA practice advisory states that FiO_2 should be kept as low as clinically feasible to avoid hypoxia. When available, diluting 100% O_2 with helium offers a small advantage over an air-nitrogen mixture attributable to its higher thermal conductivity that can delay the ignition of an ETT for a few seconds. The index of flammability is reduced by only 1 – 2 %. Additionally, helium's lower density reduces the Reynolds number, increasing tendency to laminar flow and decreases resistance during turbulent flow, allowing the use of smaller ETTs.

Ignition is facilitated and combustion is more intense in oxidizer-enriched environments, which occurs with the use of either oxygen or N_2O. In its resting state, N_2O has no free oxygen. An oxygen analyser will reflect the dilution of oxygen by N_2O when the two gases are used together. However, N_2O easily exothermically dissociates, releasing heat and free oxygen. The risk of an oxygen and N_20 mixture should be considered equivalent to administering 100% oxygen.
The ASA practice advisory states that FiO_2 should be kept as low as clinically feasible to avoid hypoxia
Reducing inspired O_2 does not protect from an increased airway oxygen concentration until expired concentration also decreases, which can take several minutes when low fresh gas flows are used.

Question 13

Correct Answer

a. Decreases as ambient temperature increases

Marking Memorandum

The latent heat of vaporisation decreases as ambient temperature increases - the lower the temperature the more latent heat is needed to vaporise a substance; and is *zero* at critical temperature

The latent heat of *fusion* is the energy required to convert a solid to a liquid at a constant temperature

Heat capacity is the amount of heat required to raise the temperature of a given object by 1 Kelvin.

Question 14

Correct answer

a. Calcium does not emit a MRI signal

Marking Memorandum

The MRI signal is produced by the change in direction of atomic nuclei with an odd number of protons or neutrons when exposed to a strong magnetic field. Calcium is an even numbered element with zero spin and therefor has no intrinsic MRI signal.

Bone appears dark in a MRI image and as the calcium produces no intrinsic signal it is very good for evaluating soft tissue surrounding bone or enclosed by bone.

A pulsatile element is not a prerequisite to produce a good MRI signal. Movements such as respiration and a beating heart can interfere with good image quality and the MRI image is synchronized with respiration or an ECG to compensate for movement.

Question 15

Correct Answer

d. They can be altered with several ligands to target specific cells

Marking Memorandum

Liposomal formulations, as well as polymeric micelles, can be combined with different ligands to target specific cells (such as cancer cells) allowing for precise and specific therapy.

Polymeric micelles are a separate type of drug delivery system.

Rapid clearance of liposomes by reticuloendothelial cells is a disadvantage of this system

Liposomes are able to encapsulate both hydrophilic and hydrophobic molecules.

SBA SESSION TEN:

Question 1

Which of the following is thought not to be a mechanism of action of Paracetamol?

a. Partial mu- receptor activation
b. Anandamide reuptake inhibition
c. Serotoninergic pathway activation
d. Peroxide-dependent COX inhibition
e. Activation of the transient receptor potential vanilloid type 1

Question 2

A 55-year-old man has severe pain on gentle touching of the arm. Six months ago, the median nerve was damaged during creation of an arteriovenous fistula for dialysis. Which of the following terms best describes this phenomenon?

a. Allodynia
b. Hyperalgesia
c. Hyperpathia
d. Hypersensitivity
e. Hypaesthesia

Question 3

What is the mechanism of action of oxytocin?

a. The main mechanism of action is via calcium channels.
b. Oxytocin directly influences the formation of calcium-calmodulin complexes.
c. Repeated administration of oxytocin results in G protein receptor desensitization.
d. Prostaglandin synthesis is not involved.

Question 4

A 76 year old man is evaluated at the pre-op anaesthetic clinic for an elective hip arthroplasty. He is in atrial fibrillation (normal valves) and has been on Rivaroxaban 20 mg daily since he had a stroke three months ago. He is also hypertensive with normal renal function. What is the management of his anti-coagulation prior to surgery?

a. Stop rivaroxaban 24 hrs prior to surgery, no bridging necessary
b. Patient is too high a thromboembolic risk to stop oral anticoagulants
c. Stop rivaroxaban 24 hrs prior to surgery and bridge with therapeutic dose LMWH until day of surgery
d. Stop rivaroxaban 2 to 3 days before surgery and bridge with therapeutic dose LMWH until the day of surgery

Question 5

A 78-year-old patient with no co-morbid disease is induced with propofol for manipulation and reduction of a Colles' (wrist) fracture. Following induction her blood pressure drops to 72/44 without an appreciable tachycardia, and requires continuous doses of vasopressor to maintain her blood pressure.

Altered baroreceptor responses in the elderly result mainly from:

a. Disordered ADH and increased BNP secretion
b. Endothelial damage and nitric oxide secretion
c. Blunted transduction of stretch signals
d. Increased afterload reducing venous compliance

Question 6

Transition from the foetal circulation to the postnatal circulation at birth involves the following cardiovascular changes:

a. An increase in left atrial pressure
b. An increase in hypoxic pulmonary vasoconstriction
c. A fall in systemic vascular resistance
d. All of the above

Question 7

A 3 year old male is anaesthetised for a closed reduction and k-wiring of a supracondylar fracture. After an initial drop in temperature, approximately 90 minutes after induction the temperature has continued to fall and is now 34.9^{o}C. The most significant contributor to this ongoing loss of core body heat is:

a. Radiation
b. Convection
c. Conduction
d. Evaporation

Question 8

Light for illumination of airway structures is typically transmitted from the source to the tip of an fiberoptic endoscope by means of:

a. Achromatic prisms
b. Convergent lenses
c. Light-emitting diodes
d. Non-coherent bundles

Question 9

Cerebrospinal fluid (CSF) is critical to cerebral functioning and wellbeing:

a. CSF is largely produced in the arachnoid villi (granulations)
b. Almost the entire volume of CSF produced flows into the basal cisterns via the CSF pathways through the brainstem
c. CSF has a sodium concentration close to or slightly lower than plasma sodium
d. CSF is not an ultrafiltrate of plasma, therefore it has a much lower protein concentration that plasma

Question 10

Regarding the effect of anaesthesia on the processed EEG electrical activity:

a. An increasingly flat (even) baseline is associated with an increasing depth of anaesthesia
b. As anaesthesia depth is increased high frequency wavelengths become dominant
c. Burst suppression describes a state when the EEG is completely isoelectric
d. Increasing depth of anaesthesia is associated with increasing amplitude of the various frequency waves

Question 11

You are asked to look at the specifications for the supply of vacuum to hospital main theatre complex. Some of your findings should be that:

a. Vacuum be generated by pneumatically powered pumps utilizing the Bernoulli principle and Venturi effect.
b. Suction apparatus is connected by yellow hose with Schrader probe and non-interchangeable indexing collar to a colour coded wall unit
c. Minimum of three vacuum inlets per theatre
d. That a vacuum of 60 kPa below atmospheric pressure is generated within 20 seconds

Question 12

a. Nitrous oxide potentiates greater reduction in cortical amplitude than it increases latency of SSEP responses when used with both volatile anaesthetics and propofol TIVA
b. Patient hypothermia has little effect on MEP readings.
c. Morphine decreases MEP amplitude by 50%
d. The absence of ankle clonus on patent wake up is a reliable test that implies the patient has not incurred damage to the motor tract.

Question 13

You are the anaesthetist for an elective orthopaedic list. X-ray screening is employed intermittently during the course of surgery. Because x-rays travel in straight lines and diverges from it source, structures that need to be assessed accurately should be placed:

a. Further from the detector
b. Closer to the detector
c. Closer to the source
d. Perpendicular to the source

Question 14

A patient in septic shock is ventilated in the ICU using high airway pressures. He has the EV1000 attached to him. His blood pressure is 77/43 [56]mmHg and a heart rate of 154bpm and SaO_2 91%. The minimally invasive cardiac output monitor shows the following:

SVV 8%
SVR 643 dynes/cm^2
SvO2 60%
CO 8L/min

Which of the following would be the most appropriate treatment for this patient:

a. A crystalloid fluid bolus followed by a titrated adrenaline infusion
b. A colloid fluid bolus of fluid followed by an adrenaline infusion
c. A titrated adrenaline infusion
d. A phenylephrine infusion

Question 15

A variable-bypass isoflurane vaporizer functioning under conditions of reduced ambient/atmospheric pressure at high altitudes will produce volatile at:

a. approximately equal concentrations to sea level, but increased partial pressures
b. approximately equal partial pressures to sea level, but increased concentrations
c. reduced concentrations compared to sea level, but approximately equal partial pressures
d. reduced partial pressures compared to sea level, but approximately equal concentrations.