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The Normal ECG

P wave

- Represents the wave of depolarization that spreads from the SA node throughout the atria
- Lasts 0.08 to 0.1 seconds (80-100 ms)
- The isoelectric period after the P wave represents the time in which the impulse is traveling within the AV node

P-R interval

- Time from the onset of the P wave to the beginning of the QRS complex
- Ranges from 0.12 to 0.20 seconds in duration
- Represents the time between the onset of atrial depolarization and the onset of ventricular depolarization

QRS complex

- Represents ventricular depolarization
- Duration of the QRS complex is normally 0.06 to 0.1 seconds

ST segment

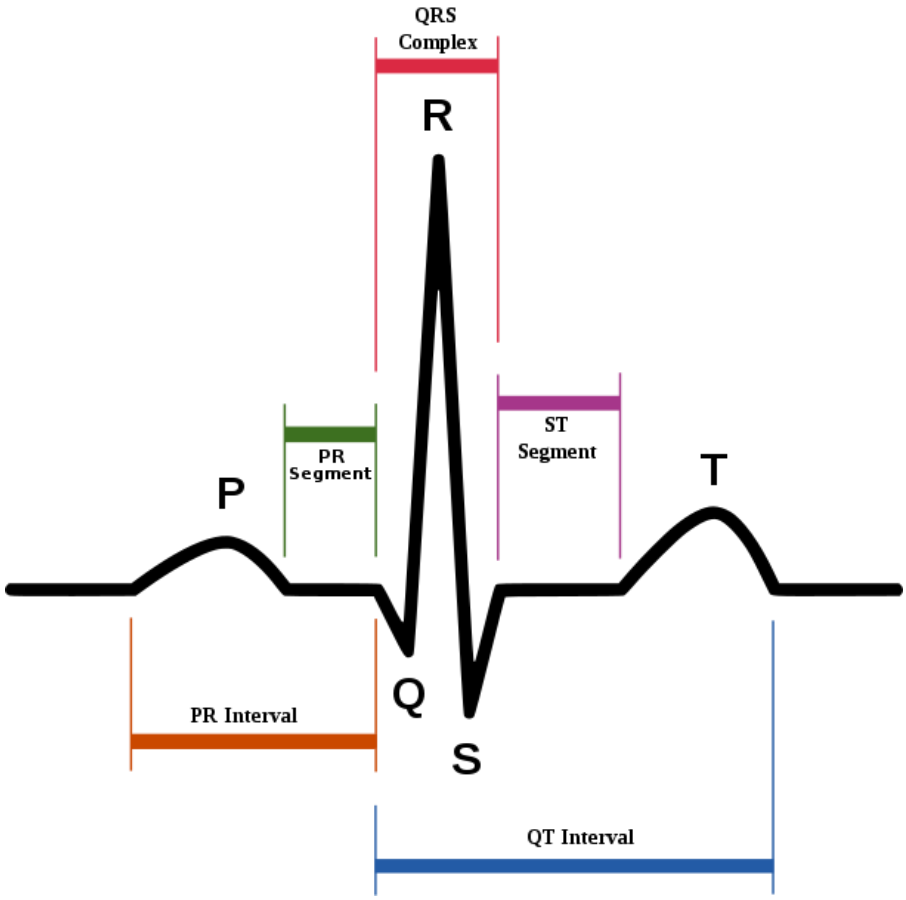
- Isoelectric period following the QRS
- Represents period which the entire ventricle is depolarized and roughly corresponds to the plateau phase of the ventricular action potential

T wave

- Represents ventricular repolarization and is longer in duration than depolarization
- A small positive U wave may follow the T wave which represents the last remnants of ventricular repolarization.

Q-T interval

- Represents the time for both ventricular depolarization and repolarization to occur, and therefore roughly estimates the duration of an average ventricular action potential.
- Interval ranges from 0.2 to 0.4 seconds depending upon heart rate.
- At high heart rates, ventricular action potentials shorten in duration, which decreases the Q-T interval. Therefore, the Q-T interval is expressed as a "corrected Q-T (QTc)" by taking the Q-T interval and dividing it by the square root of the R-R interval (interval between ventricular depolarizations). This allows an assessment of the Q-T interval that is independent of heart rate.
- Normal corrected Q-Tc interval is less than 0.44 seconds.



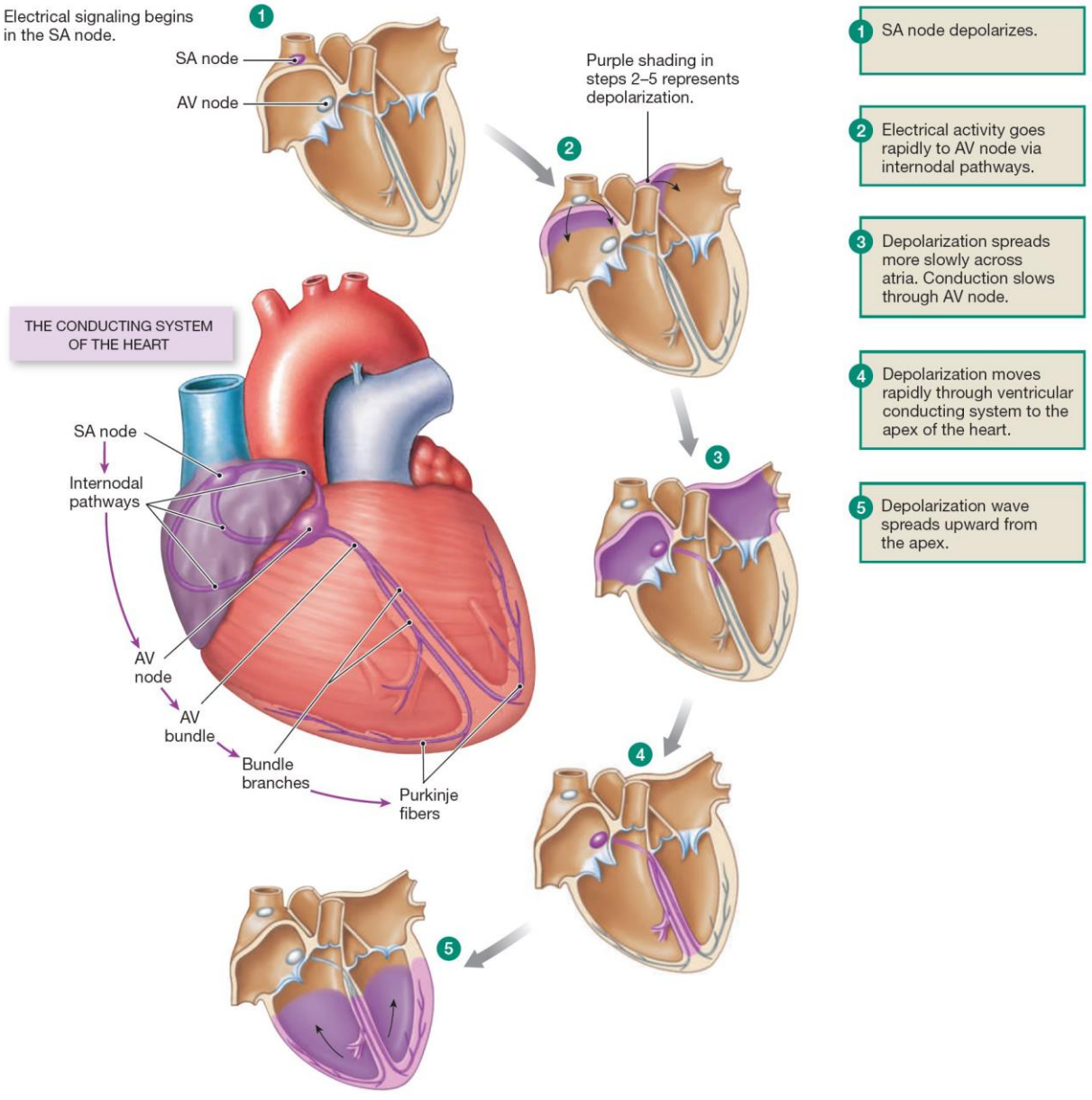
Cardiac Physiology

- The heart has four chambers ejecting blood into both low pressure and high pressure systems.
- The pumps generate pressures of between 0-25mmHg on the right side and 0-120 mmHg on the left.
- At rest diastole comprises 2/3 of the cardiac cycle.
- The product of the frequency of heart rate and stroke volume combine to give the cardiac output which is typically 5-6L per minute.

Electrical properties

- Intrinsic myogenic rhythm within cardiac myocytes means that even the denervated heart is capable of contraction.
- In the normal situation the cardiac impulse is generated in the sino atrial node in the right atrium and conveyed to the ventricles via the atrioventricular node.
- The sino atrial node is also capable of spontaneous discharge and in the absence of background vagal tone will typically discharge around 100x per minute. Hence the higher resting heart rate found in cardiac transplant cases. In the SA and AV nodes the resting membrane potential is lower than in surrounding cardiac cells and will slowly depolarise from -70mV to around -50mV at which point an action potential is generated.
- Differences in the depolarisation slopes between SA and AV nodes help to explain why the SA node will depolarise first. The cells have a refractory period during which they cannot be re-stimulated and this period allows for adequate ventricular filling. In pathological tachycardic states this time period is overridden and inadequate ventricular filling may then occur, cardiac output falls and syncope may ensue.

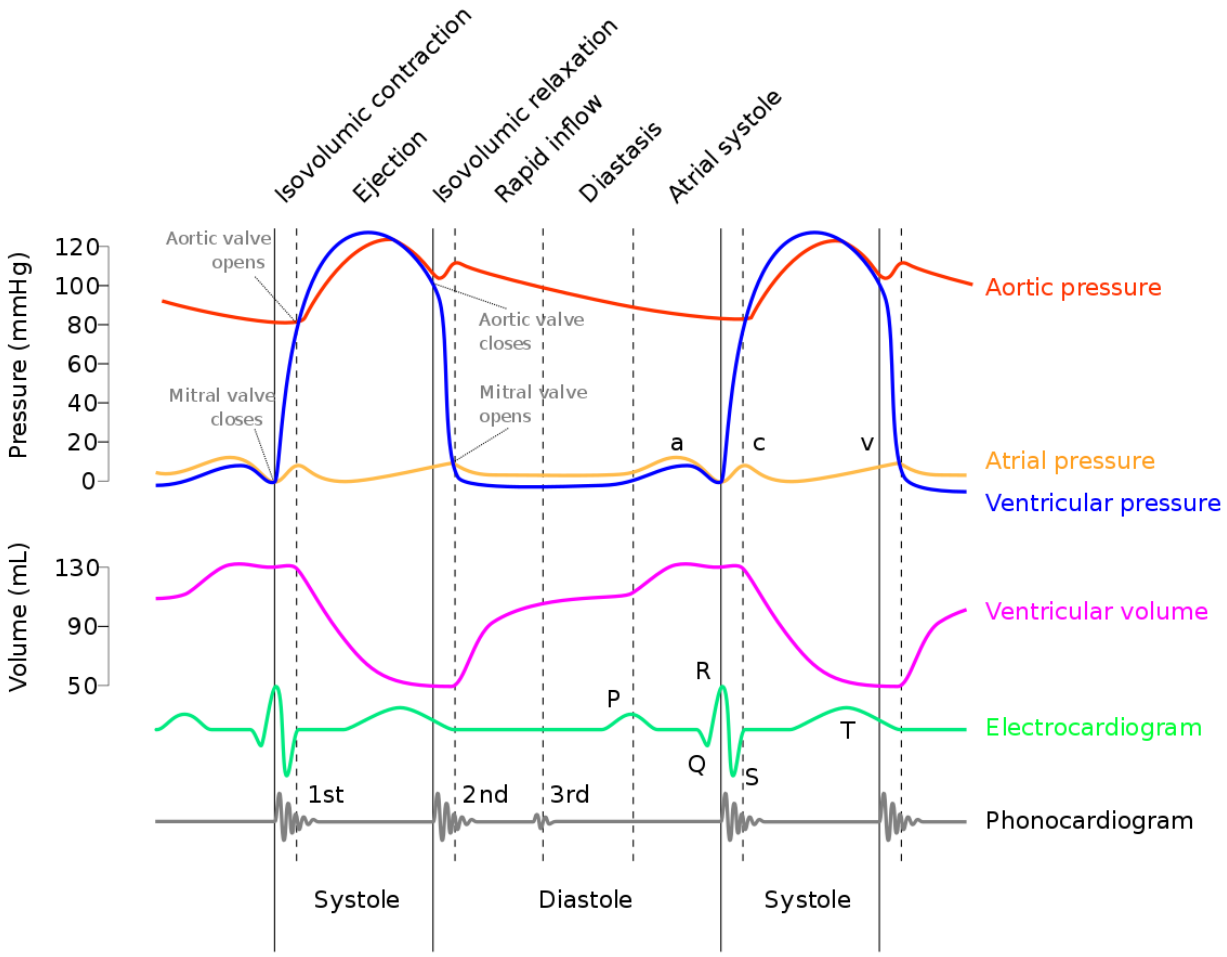
Parasympathetic fibres project to the heart via the vagus and will release acetylcholine. Sympathetic fibres release nor adrenaline and circulating adrenaline comes from the adrenal medulla. Noradrenaline binds to β 1 receptors in the SA node and increases the rate of pacemaker potential depolarisation.



Cardiac cycle

- **Mid diastole**: AV valves open. Ventricles hold 80% of final volume. Outflow valves shut. Aortic pressure is high.
- **Late diastole**: Atria contract. Ventricles receive 20% to complete filling. Typical end diastolic volume 130-160ml.
- **Early systole**: AV valves shut. Ventricular pressure rises. Isovolumetric ventricular contraction. AV Valves bulge into atria (c-wave). Aortic and pulmonary pressure exceeded- blood is ejected. Shortening of ventricles pulls atria downwards and drops intra atrial pressure (x-descent).
- **Late systole**: Ventricular muscles relax and ventricular pressures drop. Although ventricular pressure drops the aortic pressure remains constant owing to peripheral vascular resistance and elastic property of the aorta. Brief period of retrograde flow that occurs in aortic recoil shuts the aortic valve. Ventricles will contain 60ml end systolic volume. The average stroke volume is 70ml (i.e. Volume ejected).
- **Early diastole**: All valves are closed. Isovolumetric ventricular relaxation occurs. Pressure wave associated with closure of the aortic valve increases aortic pressure. The pressure dip before this rise can be seen on arterial waveforms and is called the incisura. During systole the atrial pressure increases such that it is now above zero (v- wave). Eventually atrial pressure exceeds ventricular pressure and AV valves open - atria empty passively into ventricles and atrial pressure falls (y -descent)

The negative atrial pressures are of clinical importance as they can allow air embolization to occur if the neck veins are exposed to air. This patient positioning is important in head and neck surgery to avoid this occurrence if veins are inadvertently cut, or during CVP line insertion.



Mechanical properties

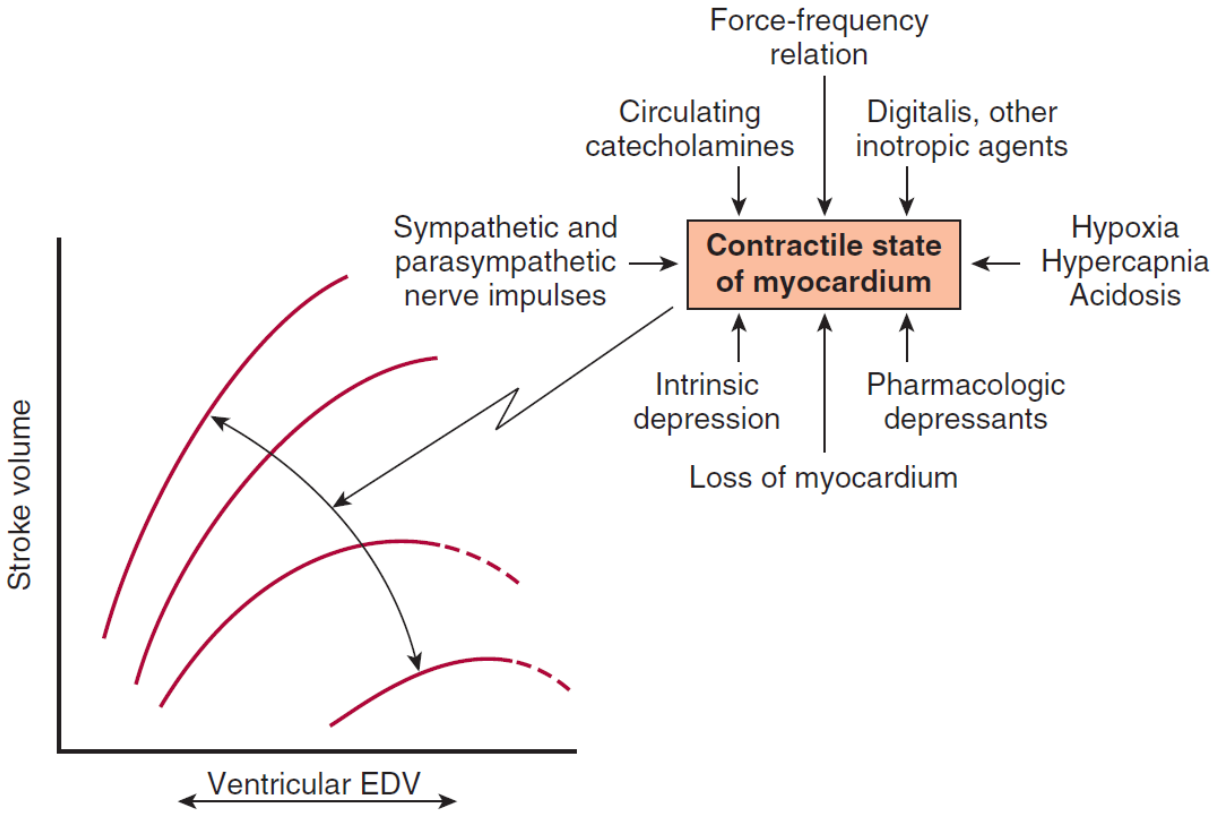
- Preload = end diastolic volume
- Afterload = aortic pressure

It is important to understand the principles of **Laplace's law** in surgery.

- It states that for hollow organs with a circular cross section, the total circumferential wall tension depends upon the circumference of the wall, multiplied by the thickness of the wall and on the wall tension.
- The total luminal pressure depends upon the cross sectional area of the lumen and the transmural pressure. Transmural pressure is the internal pressure minus external pressure and at equilibrium the total pressure must counterbalance each other.
- In terms of cardiac physiology, the law explains that the rise in ventricular pressure that occurs during the ejection phase is due to physical change in heart size. It also explains why a dilated diseased heart will have impaired systolic function.

Starlings law

- Increase in end diastolic volume will produce larger stroke volume.
- This occurs up to a point beyond which cardiac fibres are excessively stretched and stroke volume will fall once more. It is important for the regulation of cardiac output in cardiac transplant patients who need to increase their cardiac output.



Effect of changes in myocardial contractility on the Frank-Starling curve. The curve shifts downward and to the right as contractility is decreased. The major factors influencing contractility are summarized on the right. The dashed lines indicate portions of the ventricular function curves where maximum contractility has been exceeded; that is, they identify points on the "descending limb" of the Frank-Starling curve. EDV, end-diastolic volume.

Baroreceptor reflexes

- Baroreceptors located in aortic arch and carotid sinus.
- Aortic baroreceptor impulses travel via the vagus and from the carotid via the glossopharyngeal nerve.
- They are stimulated by arterial stretch.
- Even at normal blood pressures they are tonically active.
- Increase in baroreceptor discharge causes:
    - Increased parasympathetic discharge to the SA node.
    - Decreased sympathetic discharge to ventricular muscle causing decreased contractility and fall in stroke volume.
    - Decreased sympathetic discharge to venous system causing increased compliance.
    - Decreased peripheral arterial vascular resistance

Atrial stretch receptors

- Located in atria at junction between pulmonary veins and vena cava.
- Stimulated by atrial stretch and are thus low pressure sensors.
- Increased blood volume will cause increased parasympathetic activity.
- Very rapid infusion of blood will result in increase in heart rate mediated via atrial receptors: the **Bainbridge reflex**.
- Decreases in receptor stimulation results in increased sympathetic activity this will decrease renal blood flow-decreases GFR-decreases urinary sodium excretion-renin secretion by juxtaglomerular apparatus-Increase in angiotensin II.
- Increased atrial stretch will also result in increased release of atrial natriuretic peptide.

Jugular Venous Pressure (JVP)

As well as providing information on right atrial pressure, the jugular vein waveform may provide clues to underlying valvular disease. A non-pulsatile JVP is seen in superior vena caval obstruction. Kussmaul's sign describes a paradoxical rise in JVP during inspiration seen in constrictive pericarditis

'a' wave = atrial contraction

- large if atrial pressure e.g. tricuspid stenosis, pulmonary stenosis, pulmonary hypertension
- absent if in atrial fibrillation

Cannon 'a' waves

- caused by atrial contractions against a closed tricuspid valve
- are seen in complete heart block, ventricular tachycardia/ectopics, nodal rhythm, single chamber ventricular pacing

'c' wave

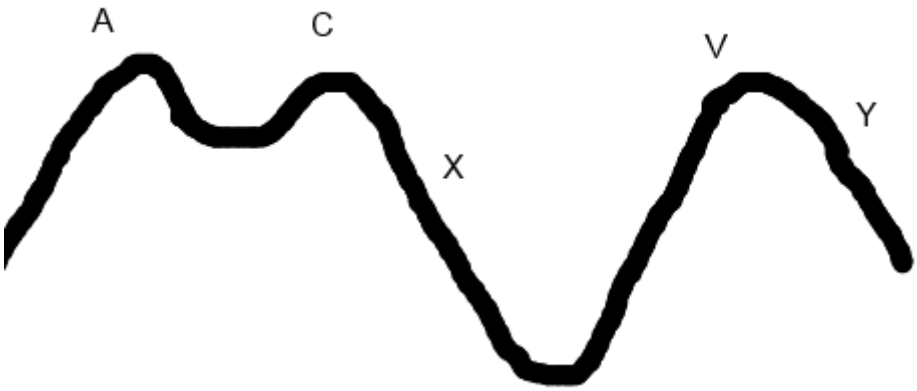
- closure of tricuspid valve
- not normally visible

'v' wave

- due to passive filling of blood into the atrium against a closed tricuspid valve
- giant v waves in tricuspid regurgitation

'x' descent = fall in atrial pressure during ventricular systole

'y' descent = opening of tricuspid valve



JVP
3 Upward deflections and 2 downward deflections

Upward deflections
***a wave** = atrial contraction*
***c wave** = ventricular contraction*
***v wave** = atrial venous filling*

Downward deflections
***x wave** = atrium relaxes and tricuspid valve moves down*
***y wave** = ventricular filling*

***Absent a waves** = Atrial fibrillation*
***Large a waves** = Any cause of right ventricular hypertrophy, tricuspid stenosis*
***Cannon waves** (extra-large a waves) = Complete heart block*
***Prominent v waves** = Tricuspid regurgitation*
***Slow y descent** = Tricuspid stenosis, right atrial myxoma*
***Steep y descent** = Right ventricular failure, constrictive pericarditis, tricuspid regurgitation*

Electrical Activity of the Heart

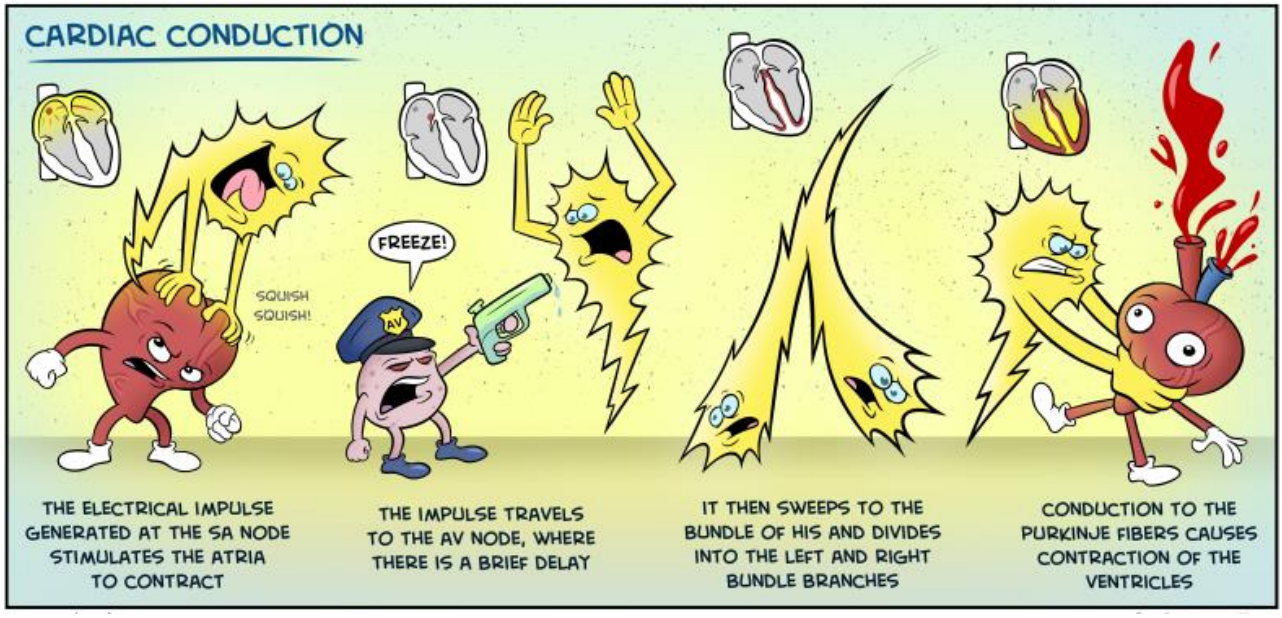
Myocardial action potential

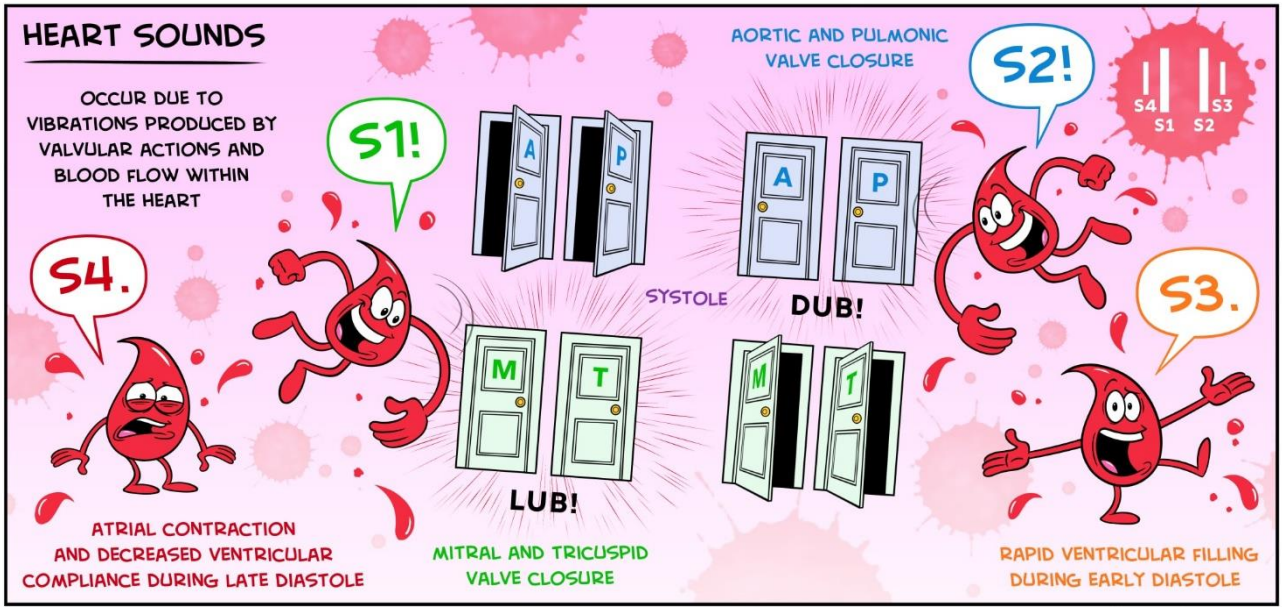
Phase	Description	Mechanism
0	Rapid depolarisation	Rapid sodium influx These channels automatically deactivate after a few ms
1	Early repolarisation	Efflux of potassium
2	Plateau	Slow influx of calcium
3	Final repolarisation	Efflux of potassium
4	Restoration of ionic concentrations	Resting potential is restored by Na^+/K^+ ATPase There is slow entry of Na^+ into the cell decreasing the potential difference until the threshold potential is reached, triggering a new action potential

NB Cardiac muscle remains contracted 10-15 times longer than skeletal muscle

Conduction velocity

Atrial conduction	Spreads along ordinary atrial myocardial fibres at 1 m/sec
AV node conduction	0.05 m/sec
Ventricular conduction	Purkinje fibres are of large diameter and achieve velocities of 2-4 m/sec (this allows a rapid and coordinated contraction of the ventricles





Inotropes and Cardiovascular Receptors

Inotropes are a class of drugs which work primarily by increasing cardiac output. They should be distinguished from vasoconstrictor drugs which are used specifically when the primary problem is peripheral vasodilatation.

Catecholamine type agents are commonly used and work by increasing cAMP levels by adenylate cyclase stimulation. This in turn intracellular calcium ion mobilisation and thus the force of contraction. Adrenaline works as a beta adrenergic receptor agonist at lower doses and an alpha receptor agonist at higher doses. Dopamine causes dopamine receptor mediated renal and mesenteric vascular dilatation and beta 1 receptor agonism at higher doses. This results in increased cardiac output. Since both heart rate and blood pressure are raised, there is less overall myocardial ischaemia. Dobutamine is a predominantly beta 1 receptor agonist with weak beta 2 and alpha receptor agonist properties. Noradrenaline is a catecholamine type agent and predominantly acts as an alpha receptor agonist and serves as a peripheral vasoconstrictor.

Phosphodiesterase inhibitors such as milrinone act specifically on the cardiac phosphodiesterase and increase cardiac output.

Inotrope	Cardiovascular receptor action
Adrenaline	α-1, α-2, β-1, β-2
Noradrenaline	α-1,(α-2), (β-1), (β-2)
Dobutamine	β-1, (β 2)
Dopamine	(α-1), (α-2), (β-1), D-1,D-2

Minor receptor effects in brackets

Effects of receptor binding

α-1, α-2	Vasoconstriction
β-1	Increased cardiac contractility and HR
β-2	Vasodilatation
D-1	Renal and spleen vasodilatation
D-2	Inhibits release of noradrenaline

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Shock

Shock occurs when there is insufficient tissue perfusion.

Septic shock

Septic shock is a major problem and those patients with severe sepsis have a mortality rate in excess of 40%. In those who are admitted to intensive care mortality ranges from 6% with no organ failure to 65% in those with 4 organ failure.

Sepsis is **defined as an infection that triggers a particular Systemic Inflammatory Response Syndrome (SIRS).** This is characterised by body temperature outside 36 ^{o}C - 38 ^{o} C, HR >90 beats/min, respiratory rate >20/min, WBC count >12,000/mm^3 or < 4,000/mm^3, altered mental state or hyperglycaemia (in absence of diabetes).

Patients with infections and two or more elements of SIRS meet the diagnostic criteria for sepsis. Those with organ failure have severe sepsis and those with refractory hypotension -septic shock.

During the septic process there is marked activation of the immune system with **extensive cytokine release**. This may be coupled with or triggered by systemic circulation of bacterial toxins. These all cause endothelial cell damage and neutrophil adhesion. The overall hallmarks are thus those of **excessive inflammation, coagulation and fibrinolytic suppression**.

The surviving sepsis campaign (2012) highlights the following key areas for attention:

- Prompt administration of antibiotics to cover all likely pathogens coupled with a rigorous search for the source of infection.
- Haemodynamic stabilisation. Many patients are hypovolaemic and require aggressive fluid administration. Aim for CVP 8-12 cm H_2O, MAP >65mmHg.
- Modulation of the septic response. This includes manoeuvres to counteract the changes and includes measures such as tight glycaemic control. The routine use of steroids is not advised.

In surgical patients, the main groups with septic shock include those with anastomotic leaks, abscesses and extensive superficial infections such as necrotising fasciitis. When performing surgery the aim should be to undertake the minimum necessary to restore physiology. These patients do not fare well with prolonged surgery. Definitive surgery can be more safely undertaken when physiology is restored and clotting in particular has been normalised.

Haemorrhagic shock

The average adult blood volume comprises 7% of body weight. Thus in the 70 Kg adult this will equate to 5 litres. This changes in children (8-9% body weight) and is slightly lower in the elderly.

Parameter	Class I	Class II	Class III	Class IV
Blood loss ml	<750ml	750-1500ml	1500-2000ml	>2000ml
Blood loss %	<15%	15-30%	30-40%	>40%
Pulse rate	<100	>100	>120	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Respiratory rate	14-20	20-30	30-40	>35
Urine output	>30ml	20-30ml	5-15ml	<5ml
Symptoms	Normal	Anxious	Confused	Lethargic

Decreasing blood pressure during haemorrhagic shock causes organ hypoperfusion and relative myocardial ischaemia. The cardiac index gives a numerical value for tissue oxygen delivery and is given by the equation: **Cardiac index= Cardiac output/ body surface area**. Where Hb is haemoglobin concentration in blood and SaO_2 the saturation and PaO_2 the partial pressure of oxygen. Detailed knowledge of this equation is required for the MRCS Viva but not for part A, although you should understand the principle.

In patients suffering from trauma the most likely cause of shock is haemorrhage. However, the following may also be the cause or occur concomitantly:

- Tension pneumothorax
- Spinal cord injury
- Myocardial contusion
- Cardiac tamponade

When assessing trauma patients, it is worth remembering that in order to generate a palpable femoral pulse an arterial pressure of >65mmHg is required.

Once bleeding is controlled and circulating volume normalised the levels of transfusion should be to maintain a Hb of 7-8 in those with no risk factors for tissue hypoxia and Hb 10 for those who have such risk factors.

Neurogenic shock

This occurs most often following a **spinal cord transection**, usually at a high level. There is resultant interruption of the autonomic nervous system. The result is either **decreased sympathetic tone or increased parasympathetic tone**, the effect of which is a decrease in peripheral vascular resistance mediated by marked vasodilation.

This results in decreased preload and thus decreased cardiac output (Starlings law). There is decreased peripheral tissue perfusion and shock is thus produced. In contrast with many other types of shock peripheral vasoconstrictors are used to return vascular tone to normal.

Cardiogenic shock

In medical patients the main cause is **ischaemic heart disease**. In the traumatic setting direct myocardial trauma or contusion is more likely. Evidence of ECG changes and overlying sternal fractures or contusions should raise the suspicion of injury. Treatment is largely supportive and transthoracic echocardiography should be used to determine evidence of pericardial fluid or direct myocardial injury. The measurement of troponin levels in trauma patients may be undertaken but they are less useful in delineating the extent of myocardial trauma than following MI.

In cardiogenic shock pulmonary pressures are often high. This is the basis for the use of venodilators in the treatment of pulmonary oedema.

When cardiac injury is of a blunt nature and is associated with cardiogenic shock the right side of the heart is the most likely site of injury with chamber and or valve rupture. These patients require surgery to repair these defects and will require cardiopulmonary bypass to achieve this. Some may require intra-aortic balloon pump as a bridge to surgery.

Anaphylactic shock

Anaphylaxis may be defined as a severe, life-threatening, generalised or systemic hypersensitivity reaction.

Anaphylaxis is one of the few times when you would not have time to look up the dose of a medication. The Resuscitation Council guidelines on anaphylaxis have recently been updated. Adrenaline is by far the most important drug in anaphylaxis and should be given as soon as possible. The recommended doses for adrenaline, hydrocortisone and chlorpheniramine are as follows:

	Adrenaline	Hydrocortisone	Chlorpheniramine
< 6 months	150 mcg (0.15ml 1 in 1,000)	25 mg	250 mcg/kg
6 months - 6 years	150 mcg (0.15ml 1 in 1,000)	50 mg	2.5 mg
6-12 years	300 mcg (0.3ml 1 in 1,000)	100 mg	5 mg
Adult and child 12 years	500 mcg (0.5ml 1 in 1,000)	200 mg	10 mg

Adrenaline can be repeated every 5 minutes if necessary. The best site for IM injection is the anterolateral aspect of the middle third of the thigh.

Common identified causes of anaphylaxis

- Food (e.g. Nuts) - the most common cause in children
- Drugs
- Venom (e.g. Wasp sting)

Fluid Compartment Physiology

Body fluid compartments comprise intracellular and extracellular compartments. The latter includes interstitial fluid, plasma and transcellular fluid.
Typical figures are based on the 70 Kg male.

Body fluid volumes

Compartment	Volume in litres	Percentage of total volume
Intracellular	28 L	60-65%
Extracellular	14 L	35-40%
Plasma	3 L	5%
Interstitial	10 L	24%
Transcellular	1 L	3%

Figures are approximate

'60-40-20 Rule' *60% total body weight is water, 40% of total body weight is intracellular fluids, 20% is extracellular fluids.*

Cerebrospinal Fluid (CSF)

The CSF fills the space between the arachnoid mater and pia mater (covering surface of the brain). The total volume of CSF in the brain is approximately 150ml. Approximately 500 ml is produced by the ependymal cells in the choroid plexus (70%), or blood vessels (30%). It is reabsorbed via the arachnoid granulations which project into the venous sinuses.

Circulation

1. Lateral ventricles (via foramen of Munro)
2. 3rd ventricle
3. Cerebral aqueduct (aqueduct of Sylvius)
4. 4th ventricle (via foramina of Magendie and Luschka)
5. Subarachnoid space
6. Reabsorbed into the venous system via arachnoid granulations into superior sagittal sinus

Composition

- Glucose: 50-80mg/dl
- Protein: 15-40 mg/dl
- Red blood cells: Nil
- White blood cells: 0-3 cells/ mm^3

Cerebral perfusion pressure

The cerebral perfusion pressure (CPP) is defined as being the net pressure gradient causing blood flow to the brain. The CPP is tightly auto regulated to maximise cerebral perfusion. A sharp rise in CPP may result in a rising ICP, a fall in CPP may result in cerebral ischaemia. It may be calculated by the following equation:

CPP = Mean arterial pressure - Intra cranial pressure

$MAP = \text{Diastolic pressure} + \frac{1}{3}(\text{Systolic pressure} - \text{Diastolic pressure})$

Following trauma, the CPP has to be carefully controlled and the may require invasive monitoring of the ICP and MAP.

Arterial Blood Gas (ABG) Interpretation

In ALS training, a 5 step approach to ABG interpretation is advocated.

1. How is the patient?

2. Is the patient hypoxaemic?

The PaO_2 on air should be 10.0-13.0 kPa.

3. Is the patient acidaemic (pH <7.35) or alkalaemic (pH >7.45)

4. What has happened to the $PaCO_2$?

If there is acidaemia, an elevated $PaCO_2$ will account for this.

5. What is the bicarbonate level or base excess?

A metabolic acidosis will have a low bicarbonate level and a low base excess (< -2 mmol).

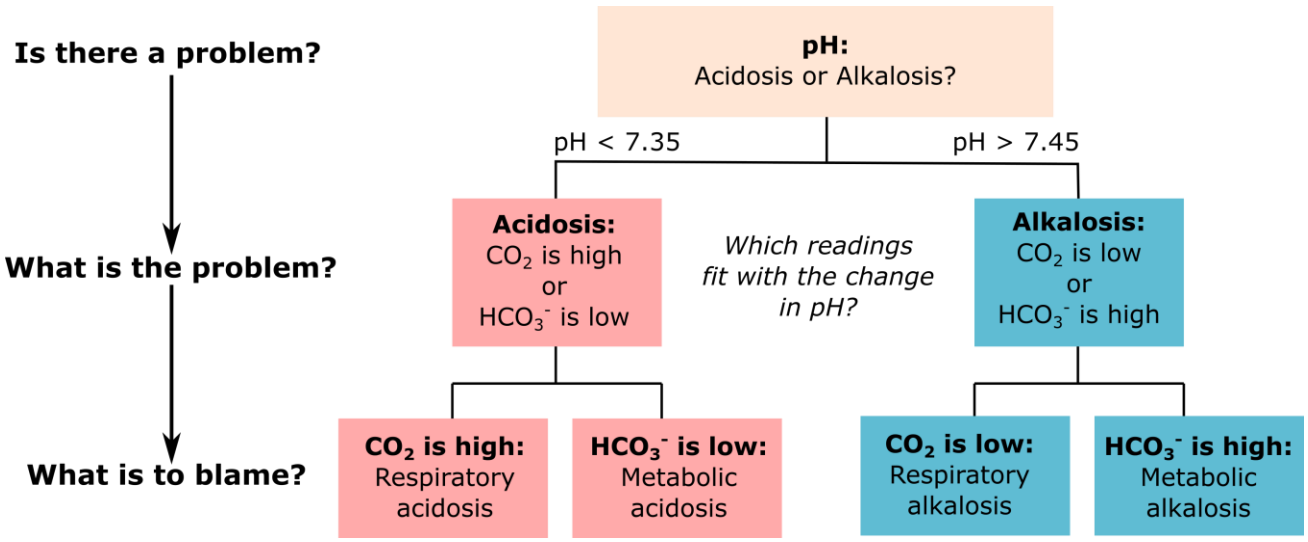
A metabolic alkalosis will have a high bicarbonate and a high base excess (> +2 mmol).

pH	7.35 – 7.45
Sa02	93 – 100%
Pa02	>10.6kPa* (75 – 100mmHg)
PaC02	4.7 – 6kPa* (35 – 45mmHg)
BE	±2mmol/L
HC03	22 – 26mmol/L

*1kPa = 7.5mmHg.
p stands for the 'partial pressure of…'

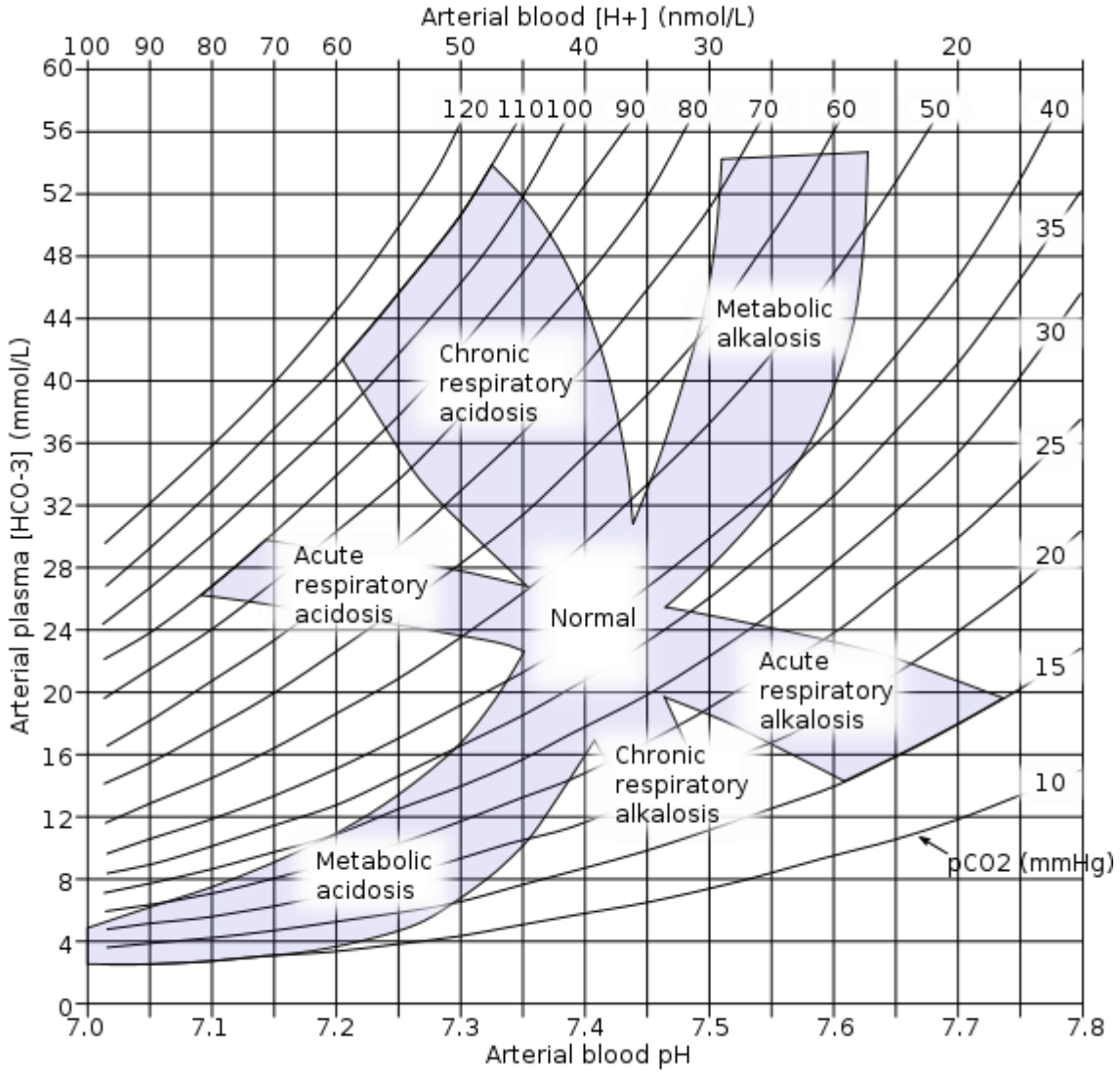
	Acidic	*Normal*	*Alkaline*
PH	< 7.35	7.35 – 7.45	> 7.45
HCO3	< 22	22 – 26	> 26
PaCO2	> 45	4.7 – 6kPa* (35 – 45mmHg)	< 35

All values in the middle column →	Normal
All values in the same column other than normal →	Mixed
2 values in one column and one in normal →	Uncompensated
2 values in one column and one in opposite →	Partially compensated
PH in normal and other values in different column →	Fully compensated



Disorders of Acid - Base Balance

Disorders of acid- base balance are often covered in the MRCS part A, both in the SBA and EMQ sections.



1- Metabolic acidosis

- This is the most common surgical acid - base disorder.
- Reduction in plasma bicarbonate levels.
- Two mechanisms:
  - Gain of strong acid (e.g. diabetic ketoacidosis)
  - Loss of base (e.g. from bowel in diarrhoea)

Classified according to the anion gap, this can be calculated by: ***$(Na^+ + K^+) - (Cl^- + HCO_3^-)$****. If a question supplies the chloride level, then this is often a clue that the anion gap should be calculated. The normal range = 8-16 mmol/L*

Normal anion gap (= hyperchloraemic metabolic acidosis)

- Gastrointestinal bicarbonate loss: diarrhoea, ureterosigmoidostomy, fistula
- Renal tubular acidosis
- Drugs: e.g. acetazolamide
- Ammonium chloride injection
- Addison's disease

Raised anion gap

- Lactate: shock, hypoxia
- Ketones: diabetic ketoacidosis, alcohol
- Urate: renal failure
- Acid poisoning: salicylates, methanol

The anion gap is calculated by:
(sodium + potassium) - (bicarbonate + chloride)

A normal anion gap is 4 – 12 mmol/L

It is useful to consider in patients with a metabolic acidosis:

Metabolic acidosis secondary to high lactate levels may be subdivided into **two types**:

- Lactic acidosis type A: (Perfusion disorders e.g. Shock, hypoxia, burns)
- Lactic acidosis type B: (Metabolic e.g. metformin toxicity)

2- Metabolic alkalosis

- Usually caused by a rise in plasma bicarbonate levels.
- Rise of bicarbonate above 24 mmol/L will typically result in renal excretion of excess bicarbonate.
- Caused by a loss of hydrogen ions or a gain of bicarbonate. It is due mainly to problems of the kidney or gastrointestinal tract

Causes

- Vomiting / aspiration (e.g. Peptic ulcer leading to pyloric stenosis, nasogastric suction)
- Diuretics
- Liquorice, carbenoxolone
- Hypokalaemia
- Primary hyperaldosteronism
- Cushing's syndrome
- Bartter's syndrome
- Congenital adrenal hyperplasia

Mechanism of metabolic alkalosis

- Activation of renin-angiotensin II-aldosterone (RAA) system is a key factor
- Aldosterone causes reabsorption of Na^+ in exchange for H^+ in the distal convoluted tubule
- ECF depletion (vomiting, diuretics) → Na^+ and Cl^- loss → activation of RAA system → raised aldosterone levels
- In hypokalaemia, K^+ shift from cells → ECF, alkalosis is caused by shift of H^+ into cells to maintain neutrality

3- Respiratory acidosis

- Rise in carbon dioxide levels usually as a result of alveolar hypoventilation
- Renal compensation may occur leading to *Compensated respiratory acidosis*

Causes

- COPD
- Decompensation in other respiratory conditions e.g. Life-threatening asthma / pulmonary oedema
- Sedative drugs: benzodiazepines, opiate overdose

4- Respiratory alkalosis

- Hyperventilation resulting in excess loss of carbon dioxide
- This will result in increasing pH

Causes

- Psychogenic: anxiety leading to hyperventilation
- Hypoxia causing a subsequent hyperventilation: pulmonary embolism, high altitude
- Early salicylate poisoning*
- CNS stimulation: stroke, subarachnoid haemorrhage, encephalitis
- Pregnancy

**Salicylate overdose leads to a mixed respiratory alkalosis and metabolic acidosis. Early stimulation of the respiratory centre leads to a respiratory alkalosis whilst later the direct acid effects of salicylates (combined with acute renal failure) may lead to an acidosis*

Coagulation Cascade

Two pathways lead to fibrin formation

Intrinsic pathway (components already present in the blood)

- Minor role in clotting
- Subendothelial damage e.g. collagen
- Formation of the primary complex on collagen by high-molecular-weight kininogen (HMWK), prekallikrein, and Factor 12
- Prekallikrein is converted to kallikrein and Factor 12 becomes activated
- Factor 12 activates Factor 11
- Factor 11 activates 9, which with its co-factor Factor 8a form the tenase complex which activates Factor 10

Extrinsic pathway (needs tissue factor released by damaged tissue)

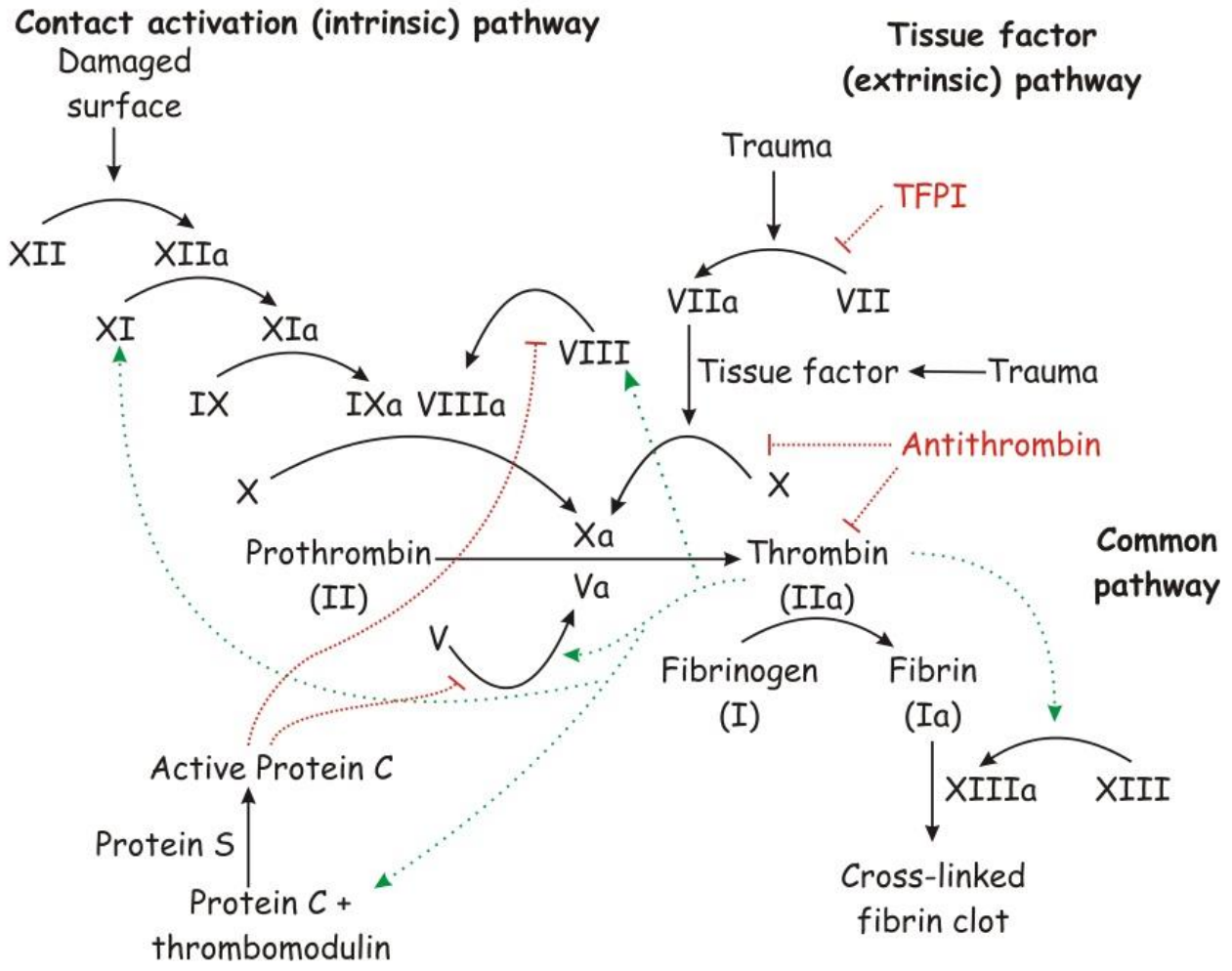
- Tissue damage
- Factor 7 binds to Tissue factor
- This complex activates Factor 9
- Activated Factor 9 works with Factor 8 to activate Factor 10

Common pathway

- Activated Factor 10 causes the conversion of prothrombin to thrombin
- Thrombin hydrolyses fibrinogen peptide bonds to form fibrin and also activates factor 8 to form links between fibrin molecules

Fibrinolysis

Plasminogen is converted to plasmin to facilitate clot resorption



Intrinsic pathway	Increased APTT	Factors 8,9,11,12
Extrinsic pathway	Increased PT	Factor 7
Common pathway	Increased APTT & PT	Factors 2,5,10
Vitamin K dependent		Factors 2,7,9,10

Interpretation Blood Clotting Test Results

Disorder	PT / INR	aPTT	Thrombin time	Platelet count	Bleeding time
Heparin	↔ / ↑	↑↑	↑↑	↔	↔
DIC	↑↑	↑↑	↑↑	↓	↑
Liver disease	↑	↑	↔ / ↑	↔ / ↓	↔ / ↑
Platelet defect	↔	↔	↔	↔	↑(↑)
Vitamin K deficiency / Warfarin	↑↑	↑	↔	↔	↔
Haemophilia	↔	↑↑	↔	↔	↔
von Willebrand's disease	↔	↑↑	↔	↔	↑(↑)
Aspirin	↔	↔	↔	↔	↑

Abnormal Coagulation

Cause	Factors affected
Heparin	Prevents activation factors 2,9,10,11
Warfarin	Affects synthesis of factors 2,7,9,10
DIC	Factors 1,2,5,8,11
Liver disease	Factors 1,2,5,7,9,10,11

Hypercoagulability

Type of thrombophilia	Features
Antithrombin deficiency	Antithrombin inactivates thrombin and factor XII a, XIa, IXa and Xa Rare defect, inherited in autosomal dominant fashion 10x increase in risk of thrombotic events Heparin may be ineffective because it works via antithrombin
Protein C and S deficiency	These are natural anticoagulants (vitamin K dependent synthesis) Protein C produced by liver Protein S produced by liver, megakaryocytes, Leydig cells and endothelial cells Protein C and S bind to form activated complex which binds to factor V Deficiency accounts for up to 5% of thrombotic episodes
Factor V Leiden	Resistance to anticoagulant effect of activated protein C May account for up to 20% or more of thrombotic episodes Prevalence of 7% in Europe Most common genetic defect accounting for DVT
Antiphospholipid syndrome	Multi organ disease Pregnancy involvement common Arterial and venous thromboses Either Lupus anticoagulant or Anti cardiolipin antibodies APTT usually prolonged Antibodies may be elevated following surgery, drugs or malignancy Need anticoagulation with INR between 3 and 4

Warfarin

Warfarin is an oral anticoagulant which inhibits the reduction of vitamin K to its active hydroquinone form, which in turn acts as a cofactor in the formation of clotting factor II, VII, IX and X (***mnemonic = 1972***) and protein C

Aid to memoire: ***WEPT***
Warfarin **E**xtrinsic **P**rothrombin **T**ime

Factors that may potentiate warfarin

- Liver disease
- P450 enzyme inhibitors, e.g.: amiodarone, ciprofloxacin
- Cranberry juice
- Drugs which displace warfarin from plasma albumin, e.g. NSAIDs
- Inhibit platelet function: NSAIDs

Side-effects

- Haemorrhage
- Teratogenic
- Skin necrosis: when warfarin is first started biosynthesis of protein C is reduced. This results in a temporary procoagulant state after initially starting warfarin, normally avoided by concurrent heparin administration. Thrombosis may occur in venules leading to skin necrosis.

Heparin

Causes the formation of complexes between antithrombin and activated **thrombin/factors 7,9,10,11 & 12**

Advantages of low molecular weight heparin (LMWH)

- Better bioavailability
- Lower risk of bleeding
- Longer half life
- Little effect on APTT at prophylactic dosages
- Less risk of HIT

Complications

- Bleeding
- Osteoporosis
- Heparin induced thrombocytopenia (HIT): occurs 5-14 days after 1st exposure
- Anaphylaxis

In surgical patients that may need a rapid return to theatre, administration of **unfractionated heparin is preferred; as low molecular weight heparins have a longer duration of action and are harder to reverse**.

(See 'Thrombophylaxis in Surgical Patients' in 'Peri-operative Care' chapter…)

Bleeding

The initial response to bleeding, even if of relatively small volume is generalised **splanchnic vasoconstriction** mediated by activation of the sympathetic nervous system. This process of vasoconstriction is usually sufficient to maintain renal perfusion and cardiac output if the volume of blood lost is small. Over the following hours the circulating fluid volume is restored and normal haemodynamics resume. Loss of greater volumes of blood will typically result in activation in the renin angiotensin system (see diagram later).

Where the source of bleeding ceases these physiological measures will restore circulating volume. Ongoing bleeding will result in haemorrhagic shock. Blood loss is typically quantified by the degree of shock produced as outlined later…
(See haemorrhagic shock later…)

Acute Phase Proteins

- CRP
- Procalcitonin
- Ferritin
- Fibrinogen
- Alpha-1 antitrypsin
- Caeruloplasmin
- Serum amyloid A
- Haptoglobin
- Complement

During the acute phase response, the liver decreases the production of other proteins (sometimes referred to as negative acute phase proteins). Examples include:

- albumin
- transthyretin (formerly known as prealbumin)
- transferrin
- retinol binding protein
- cortisol binding protein

Levels of CRP are commonly measured in acutely unwell patients. CRP is a protein synthesised in the liver and binds to phosphocholine in bacterial cells and on those cells undergoing apoptosis. In binding to these cells it is then able to activate the complement system. CRP levels are known to rise in patients following surgery. However, levels of greater than 150 at 48 hours post operatively are suggestive of evolving complications.

Tumour Necrosis Factor (TNF)

Tumour necrosis factor (TNF) is a pro-inflammatory cytokine with multiple roles in the immune system

TNF is secreted mainly by macrophages and has a number of effects on the immune system, acting mainly in a paracrine fashion:

- Activates macrophages and neutrophils
- Acts as co-stimulator for T cell activation
- Key mediator of bodies response to Gram negative septicaemia
- Similar properties to IL-1
- Anti-tumour effect (e.g. phospholipase activation)

TNF-alpha binds to both the p55 and p75 receptor. These receptors can induce apoptosis. It also cause activation of NFkB

Endothelial effects include increase expression of selectins and increased production of platelet activating factor, IL-1 and prostaglandins

TNF promotes the proliferation of fibroblasts and their production of protease and collagenase. It is thought fragments of receptors act as binding points in serum

Systemic effects include pyrexia, increased acute phase proteins and disordered metabolism leading to cachexia

TNF is important in the pathogenesis of rheumatoid arthritis - TNF blockers (e.g. infliximab, etanercept) are now licensed for treatment of severe rheumatoid

Calcium Homeostasis

Calcium ions are linked to a wide range of physiological processes. The largest store of bodily calcium is contained within the skeleton. Calcium levels are primarily controlled by parathyroid hormone, vitamin D and calcitonin.

Hormonal regulation of calcium

Hormone	Actions
Parathyroid hormone (PTH)	• Increase calcium levels and decrease phosphate levels • Increases bone resorption • Immediate action on osteoblasts to increase ca^{2+} in extracellular fluid • Osteoblasts produce a protein signaling molecule that activate osteoclasts which cause bone resorption • Increases renal tubular reabsorption of calcium • Increases synthesis of 1,25(OH)2D (active form of vitamin D) in the kidney which increases bowel absorption of Ca^{2+} • Decreases renal phosphate reabsorption
1,25-dihydroxycholecalciferol (the active form of vitamin D)	• Increases plasma calcium and plasma phosphate • Increases renal tubular reabsorption and gut absorption of calcium • Increases osteoclastic activity • Increases renal phosphate reabsorption
Calcitonin	• Secreted by C cells of thyroid • Inhibits intestinal calcium absorption • Inhibits osteoclast activity • Inhibits renal tubular absorption of calcium

Both growth hormone and thyroxine also play a small role in calcium metabolism.

Hypocalcaemia

The clinical history combined with parathyroid hormone levels will reveal the cause of hypocalcaemia in the majority of cases

Causes

- Vitamin D deficiency (osteomalacia)
- Acute pancreatitis
- Chronic renal failure
- Hypoparathyroidism (e.g. post thyroid/parathyroid surgery)
- Pseudohypoparathyroidism (target cells insensitive to PTH)
- Rhabdomyolysis (initial stages)
- Magnesium deficiency (due to end organ PTH resistance)

Signs & Symptoms: ***CATS** go **Numb***

- **C**onvulsions
- **A**rrhythmias
- **T**etany
- **S**pasms and stridor
- **Numb**ness in the fingers

Symptoms

- Tetany, parasthesia and confusion
- Chvostek's sign: *twitching of facial muscles in response to Tapping over facial nerve*
- Trousseau's sign: *carpopedal spasm following reduction in blood flow to the hand that is elicited by inflation blood flow cuff to 20 mmHg above systolic pressure for 3 minutes.*

Management

- Acute management of severe hypocalcaemia is with intravenous replacement. The preferred method is with intravenous calcium chloride, 10ml of 10% solution over 10 minutes
- ECG monitoring is recommended
- Further management depends on the underlying cause
- Calcium and bicarbonate should not be administered via the same route

Hypercalcaemia

Main causes

- Malignancy (most common cause in hospital in-patients)
- Primary hyperparathyroidism (commonest cause in non hospitalised patients)

Less common

- Sarcoidosis (extrarenal synthesis of calcitriol)
- Thiazides, lithium
- Immobilisation
- Paget's disease
- Vitamin A/D toxicity
- Thyrotoxicosis
- MEN
- Milk alkali syndrome

Causes 'CHIMPANZEES'
Calcium supplementation
Hyperparathyroidism
Iatrogenic (Drugs: Thiazides)
Milk Alkali syndrome
Paget disease of the bone
Acromegaly and Addison's Disease
Neoplasia
Zollinger-Ellison Syndrome (MEN Type I)
Excessive Vitamin D
Excessive Vitamin A
Sarcoidosis

Clinical features

Stones, bones, abdominal groans, and psychic moans

High serum calcium levels result in decreased neuronal excitability. Therefore, sluggish reflexes, muscle weakness and constipation may occur.

Management of Hypercalcaemia

- Free Ca is affected by pH (increased in acidosis) and plasma albumin concentration
- ECG changes include: Shortening of QT interval
- **Urgent** management is indicated if:
    - Calcium > 3.5 mmol/l
    - Reduced consciousness
    - Severe abdominal pain
    - Pre renal failure

Management:

- Airway Breathing Circulation
- Intravenous fluid resuscitation with 3-6L of 0.9% Normal saline in 24 hours
- Concurrent administration of calcitonin will also help lower calcium levels
- Medical therapy (usually if Corrected calcium >3.0mmol/l)

Bisphosphonates

- Analogues of pyrophosphate
- Prevent osteoclast attachment to bone matrix and interfere with osteoclast activity
- Inhibit bone resorption.

Agents

Drug	Side effects	Notes
IV Pamidronate	Pyrexia, Leucopaenia	Most potent agent
IV Zoledronate	Response lasts 30 days	Used for malignancy associated hypercalcaemia

Calcitonin

- Quickest onset of action however short duration (tachyphylaxis) therefore only given with a second agent.

Prednisolone

- May be given in hypercalcaemia related to sarcoidosis, myeloma or vitamin D intoxication.

Hyperkalaemia

- Plasma potassium levels are regulated by a number of factors including aldosterone, acid-base balance and insulin levels.
- Metabolic acidosis is associated with hyperkalaemia as hydrogen and potassium ions compete with each other for exchange with sodium ions across cell membranes and in the distal tubule.
- ECG changes seen in hyperkalaemia include tall-tented T waves, small P waves, widened QRS leading to a sinusoidal pattern and asystole

Causes of hyperkalaemia

- Acute renal failure
- Drugs*: K^+ sparing diuretics, ACEI, angiotensin 2 receptor blockers, spironolactone, cyclosporin, heparin**
- Metabolic acidosis
- Addison's
- Tissue necrosis / Rhabdomyolysis: burns, trauma
- Massive blood transfusion

**beta-blockers interfere with potassium transport into cells and can potentially cause hyperkalaemia in renal failure patients - remember beta-agonists, e.g. Salbutamol, are sometimes used as emergency treatment*

***both unfractionated and low-molecular weight heparin can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion*

Foods that are high in potassium

- Salt substitutes (i.e. Contain potassium rather than sodium)
- Bananas, oranges, kiwi fruit, avocado, spinach, tomatoes

Hypokalaemia

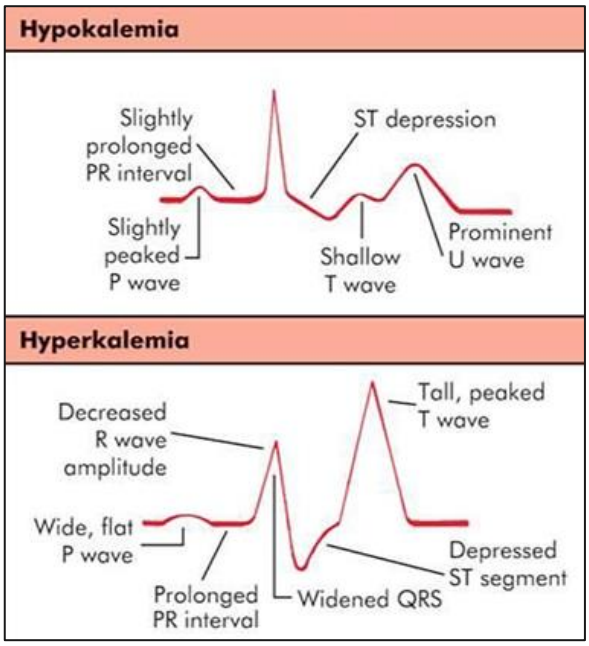
Potassium and hydrogen can be thought of as competitors. Hyperkalaemia tends to be associated with acidosis because as potassium levels rise fewer hydrogen ions can enter the cells

Hypokalaemia with alkalosis

- Vomiting
- Diuretics
- Cushing's syndrome
- Conn's syndrome (primary hyperaldosteronism)

Hypokalaemia with acidosis

- Diarrhoea
- Renal tubular acidosis
- Acetazolamide
- Partially treated diabetic ketoacidosis



ECG Features in Hypokalaemia

- U waves
- Small or absent T waves (occasionally inversion)
- Prolonged PR interval
- ST depression
- Long QT interval

*In Hypokalaemia, **U** have no **P**ot and no **T**, but a long **PR** and a long **QT**!*

Hypomagnasaemia

Cause of low magnesium

- Diuretics
- Total parenteral nutrition
- Diarrhoea
- Alcohol
- Hypokalaemia, hypocalcaemia

Features

- Paraesthesia
- Tetany
- Seizures
- Arrhythmias
- Decreased PTH secretion → hypocalcaemia
- ECG features similar to those of hypokalaemia
- Exacerbates digoxin toxicity

Hyponatraemia

This is commonly tested in the MRCS (despite most surgeons automatically seeking medical advice if this occurs!). The most common cause in surgery is the over administration of 5% dextrose.

Hyponatraemia may be caused by water excess or sodium depletion. Causes of pseudohyponatraemia include hyperlipidaemia (increase in serum volume) or a taking blood from a drip arm. Urinary sodium and osmolarity levels aid making a diagnosis.

Classification

Urinary sodium > 20 mmol/l	**Sodium depletion, renal loss** • Patient often hypovolaemic • Diuretics (thiazides) • Addison's • Diuretic stage of renal failure • SIADH (serum osmolality low, urine osmolality high, urine Na high) • Patient often euvolaemic	Mnemonic: Syndrome of **INAPP**ropriate Anti-Diuretic Hormone: **I**ncreased **Na** (sodium) **PP** (urine)
Urinary sodium < 20 mmol/l	**Sodium depletion, extra-renal loss** • Diarrhoea, vomiting, sweating • Burns, adenoma of rectum (if villous lesion and large)	
Water excess *(patient often hypervolaemic and oedematous)*	• Secondary hyperaldosteronism: CCF, cirrhosis • Reduced GFR: renal failure • IV dextrose, psychogenic polydipsia	

Management

Symptomatic Hyponatremia:
Acute hyponatraemia with Na <120: immediate therapy. Central Pontine Myelinolisis, may occur from overly rapid correction of serum sodium. Aim to correct until the Na is > 125 at a rate of 1 mEq/h. Normal saline with frusemide is an alternative method.

The sodium requirement can be calculated as follows :
(125 - serum sodium) x 0.6 x body weight = required mEq of sodium

Hyperuricaemia

- Increased levels of uric acid may be seen secondary to either increased cell turnover or reduced renal excretion of uric acid. Hyperuricaemia may be found in asymptomatic patients who have not experienced attacks of gout
- Hyperuricaemia may be associated with hyperlipidaemia and hypertension. It may also be seen in conjunction with the metabolic syndrome

Increased synthesis

- Lesch-Nyhan disease
- Myeloproliferative disorders
- Diet rich in purines
- Exercise
- Psoriasis
- Cytotoxics

Decreased excretion

- Drugs: low-dose aspirin, diuretics, pyrazinamide
- Pre-eclampsia
- Alcohol
- Renal failure
- Lead

Drugs causing hyperuricaemia as a result of reduced excretion of urate ***'CAN'T LEAP'***

- **C**yclosporin
- **A**lcohol
- **N**icotinic acid
- **T**hiazides
- **L**oop diuretics
- **E**thambutol
- **A**spirin
- **P**yrazinamide

Potassium Secretion - GI Tract

Potassium secretions

Salivary glands	Variable may be up to 60mmol/L
Stomach	10 mmol/L
Bile	5 mmol/L
Pancreas	4-5 mmol/L
Small bowel	10 mmol/L
Rectum	30 mmol/L

The above table provides average figures only and the exact composition varies depending upon the existence of disease, serum aldosterone levels and serum pH.

A key point to remember for the exam is that gastric potassium secretions are low. Hypokalaemia may occur in vomiting, usually as a result of renal wasting of potassium, not because of potassium loss in vomit.

Iron Metabolism

Absorption	• **Duodenum and upper jejunum** • About 10% of dietary iron absorbed • Fe^{2+} (ferrous iron) much better absorbed than Fe^{3+} (ferric iron) • Ferrous iron is oxidized to form ferric iron, which is combined with apoferritin to form ferritin • Absorption is regulated according to body's need • Increased by vitamin C, gastric acid • Decreased by proton pump inhibitors, tetracycline, gastric achlorhydria, tannin (found in tea)
Transport	In plasma as Fe^{3+} bound to transferrin
Storage	Ferritin (or haemosiderin) in bone marrow
Excretion	Lost via intestinal tract following desquamation

Distribution in body

Total body iron	**4g**
Haemoglobin	*70%*
Ferritin and haemosiderin	*25%*
Myoglobin	*4%*
Plasma iron	*0.1%*

Pulmonary Artery Occlusion Pressure Monitoring

The pulmonary artery occlusion pressure is an indirect measure of left atrial pressure, and thus filling pressure of the left heart. The low resistance within the pulmonary venous system allows this useful measurement to be made. The most accurate trace is made by inflating the balloon at the catheter tip and "floating" it so that it occludes the vessel. If it is not possible to occlude the vessel in this way then the measurement gained will be the pulmonary artery end diastolic pressure.

Interpretation of PAOP

PAOP	mmHg	Scenario
Normal	8-12	
Low	<5	Hypovolaemia
Low with pulmonary oedema	<5	ARDS
High	>18	Overload

When combined with measurements of systemic vascular resistance and cardiac output it is possible to accurately classify patients.

Systemic vascular resistance

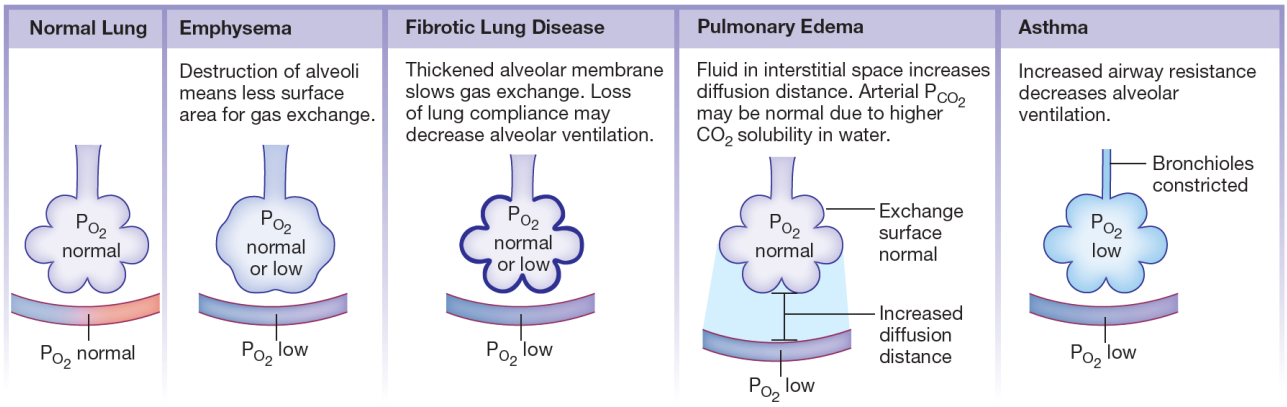
Derived from aortic pressure, right atrial pressure and cardiac output.

$$SVR = \frac{80 \times (mean\ arterial\ pressure\ -\ mean\ right\ atrial\ pressure)}{cardiac\ output}$$

Respiratory Physiology: Lung Compliance

Lung compliance is defined as change in lung volume per unit change in airway pressure

Diffusion ∝ surface area × barrier permeability/distance^2



Causes of increased compliance

- Age
- Emphysema - this is due to loss alveolar walls and associated elastic tissue

Causes of decreased compliance

- Pulmonary oedema
- Pulmonary fibrosis
- Pneumonectomy
- Kyphosis

Transfer Factor

The transfer factor describes the rate at which a gas will diffuse from alveoli into blood. Carbon monoxide is used to test the rate of diffusion. Results may be given as the total gas transfer (T_{LCO}; Transfer factor of the Lung for Carbon Monxide) or that corrected for lung volume (transfer coefficient, KCO)

Causes of a raised TLCO	Causes of a lower TLCO
• Asthma • Pulmonary Hge (Wegener's, Goodpasture's) • Left-to-right cardiac shunts • Polycythaemia • Hyperkinetic states • Male gender, exercise	• Pulmonary fibrosis • Pneumonia • Pulmonary emboli • Pulmonary oedema • Emphysema • Anaemia • Low cardiac output

***raised**: asthma, haemorrhage, left-to-right shunts, polycythaemia. **low**: everything else.*

KCO also tends to increase with age. Some conditions may cause an increased KCO with a normal or reduced TLCO

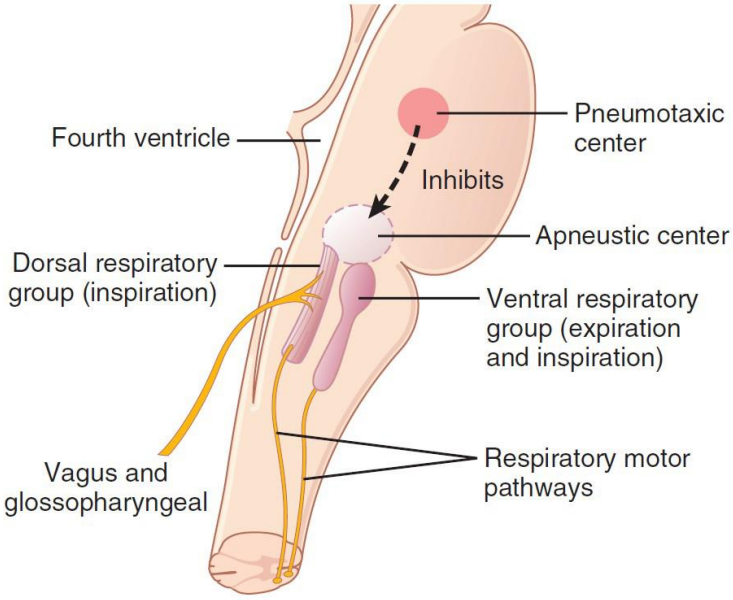
- Pneumonectomy/lobectomy
- Scoliosis / Kyphosis
- Neuromuscular weakness
- Ankylosis of costovertebral joints e.g. Ankylosing spondylitis

Control of Ventilation

- Control of ventilation is coordinated by the respiratory centres, chemoreceptors, lung receptors and muscles.
- Automatic, involuntary control of respiration occurs from the medulla.
- The respiratory centres control the respiratory rate and the depth of respiration.

Respiratory centres

Medullary respiratory centre	Inspiratory and expiratory neurones. Has ventral group which controls forced voluntary expiration and the dorsal group controls inspiration. Depressed by opiates.
Apneustic centre	Lower pons Stimulates inspiration - activates and prolongs inhalation Overridden by pneumotaxic control to end inspiration
Pneumotaxic centre	Upper pons, inhibits inspiration at a certain point. Fine tunes the respiratory rate.



Ventillatory variables

- Levels of pCO_2 most important in ventilation control
- Levels of O_2 are less important.
- Peripheral chemoreceptors: located in the bifurcation of carotid arteries and arch of the aorta. They respond to changes in reduced pO_2, increased H^+ and increased pCO_2 in ARTERIAL BLOOD.
- Central chemoreceptors: located in the medulla. Respond to increased H^+ in BRAIN INTERSTITIAL FLUID to increase ventilation. NB the central receptors are NOT influenced by O_2 levels.

Lung receptors include:

- Stretch receptors: respond to lung stretching causing a reduced respiratory rate
- Irritant receptors: respond to smoke, etc. causing bronchospasm
- J (juxtacapillary) receptors

Alveolar Ventilation

Alveolar ventilation is the volume of fresh air entering the alveoli per minute.
Alveolar ventilation = Minute ventilation - Dead space volume

Minute ventilation

Is the total volume of gas ventilated per minute.
MV (ml/min) = tidal volume x Respiratory rate (resps/min).

Dead space ventilation

Describes the volume of gas not involved in exchange in the blood.
There are **2 types:**

1. **Anatomical dead space:** 150mls
   - Volume of gas in the respiratory tree not involved in gaseous exchange: mouth, pharynx, trachea, bronchi up to terminal bronchioles
   - Measured by Fowlers method
   - **Increased by**: Standing, increased size of person, increased lung volume and drugs causing bronchodilatation e.g. Adrenaline

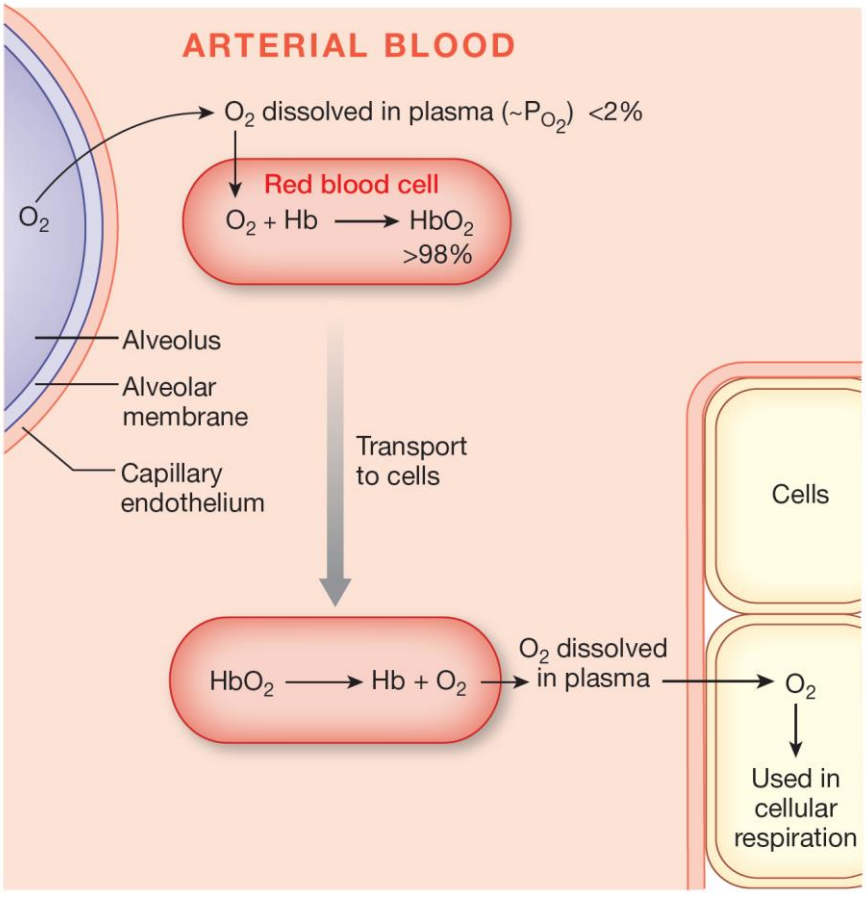
2. **Physiological dead space:** normal 150 mls,
   - Volume of gas in the alveoli and anatomical dead space not involved in gaseous exchange.
   - Increases in: Ventilation/Perfusion mismatch e.g. PE, COPD, hypotension.

Oxygen Transport

Almost all oxygen is transported within erythrocytes. It has limited solubility and only 1% is carried as solution. Therefore the amount of oxygen transported will depend upon haemoglobin concentration and its degree of saturation.

Haemoglobin

Globular protein composed of 4 subunits. Haem consists of a protoporphyrin ring surrounding an iron atom in its ferrous state. The iron can form two additional bonds; one with oxygen and the other with a polypeptide chain. There are two alpha and two beta subunits to this polypeptide chain in an adult and together these form globin. Globin cannot bind oxygen but is able to bind to carbon dioxide and hydrogen ions, the beta chains are able to bind to 2,3 diphosphoglycerate. The oxygenation of haemoglobin is a reversible reaction. The molecular shape of haemoglobin is such that binding of one oxygen molecule facilitates the binding of subsequent molecules.



Oxygen dissociation curve

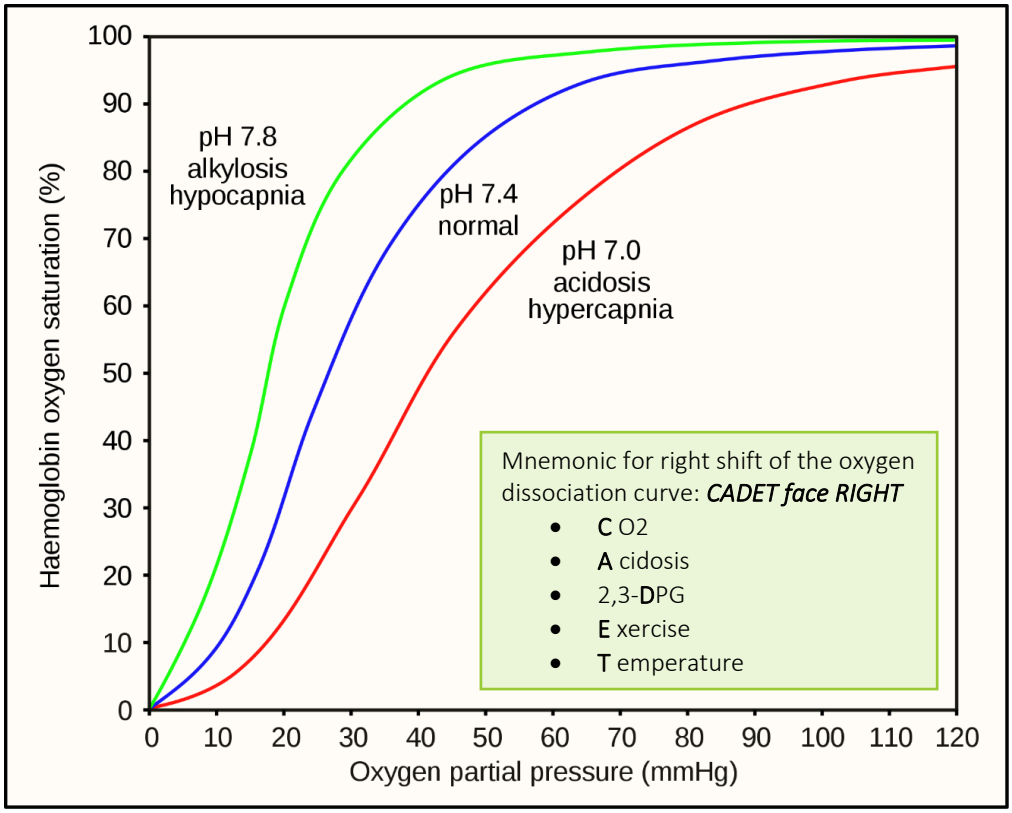
- The oxygen dissociation curve describes the relationship between the percentage of saturated haemoglobin and partial pressure of oxygen in the blood. It is not affected by haemoglobin concentration.
- Chronic anaemia causes 2, 3 DPG levels to increase, hence shifting the curve to the right

Haldane effect

- Shifts to left = for given oxygen tension there is increased saturation of Hb with oxygen i.e. Decreased oxygen delivery to tissues

Bohr effect

- Shifts to right = for given oxygen tension there is reduced saturation of Hb with oxygen i.e. Enhanced oxygen delivery to tissues



Shifts to Left = Lower oxygen delivery

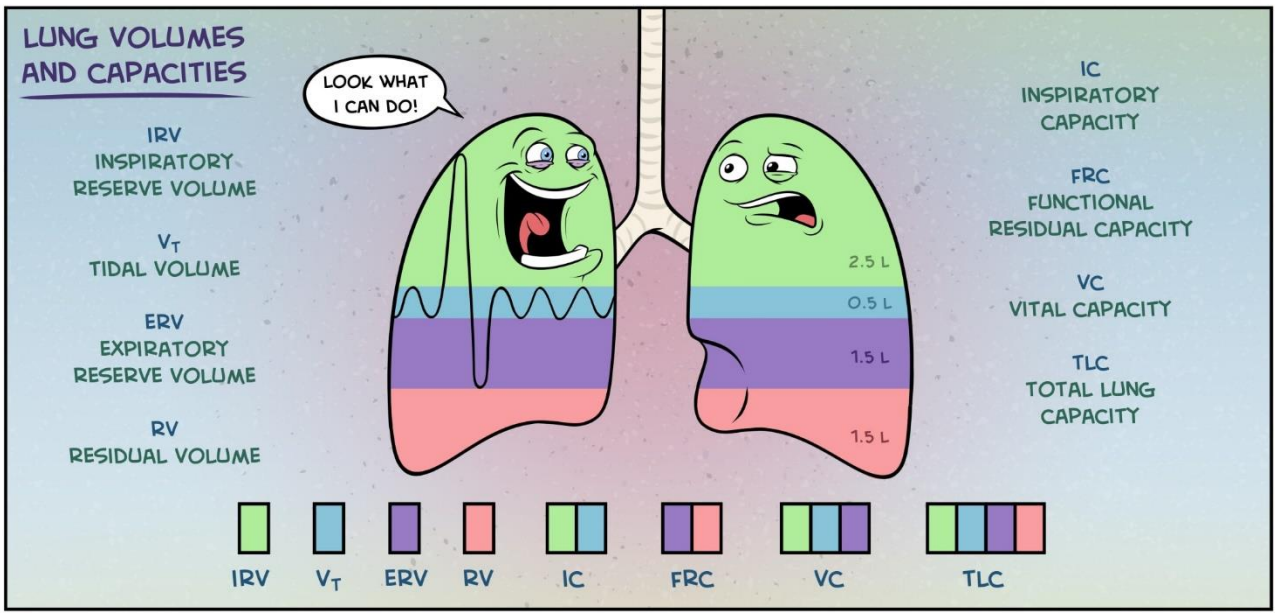
- low $[H^+]$ (alkali)
- low pCO_2
- low 2,3-DPG
- low temperature
- HbF, methaemoglobin, carboxyhaemoglobin

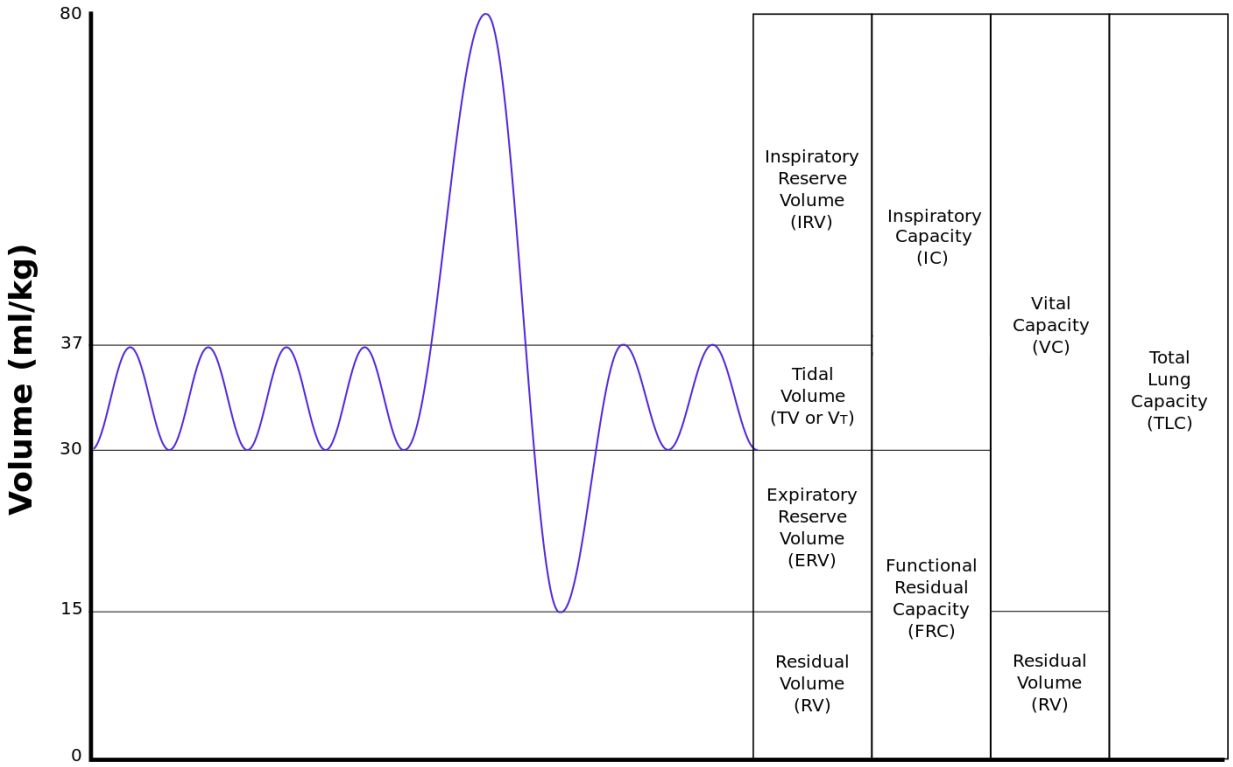
Shifts to Right = Raised oxygen delivery

- raised $[H^+]$ (acidic)
- raised pCO_2
- raised 2,3-DPG (diphosphoglycerate)
- raised temperature

Lung Volumes

Tidal volume (TV)	• Is the volume of air inspired and expired during each ventilatory cycle at rest. • It is normally 500mls in males and 340mls in females.
Inspiratory reserve volume (IRV)	• Is the maximum volume of air that can be forcibly inhaled following a normal inspiration. 3000mls.
Expiratory reserve volume (ERV)	• Is the maximum volume of air that can be forcibly exhaled following a normal expiration. 1000mls.
Residual volume (RV)	• Is that volume of air remaining in the lungs after a maximal expiration. • RV = FRC - ERV. 1500mls.
Functional residual capacity (FRC)	• Is the volume of air remaining in the lungs at the end of a normal expiration. • FRC = RV + ERV. 2500mls.
Vital capacity (VC)	• Is the maximal volume of air that can be forcibly exhaled after a maximal inspiration. • VC = TV + IRV + ERV. 4500mls in males, 3500mls in females.
Total lung capacity (TLC)	• Is the volume of air in the lungs at the end of a maximal inspiration. • TLC = FRC + TV + IRV = VC + RV. 5500-6000mls.
Forced vital capacity (FVC)	• The volume of air that can be maximally forcefully exhaled.





Parathyroid Hormone

Parathyroid hormone is secreted by the chief cells of the parathyroid glands. It acts to increase serum calcium concentration by stimulation of the PTH receptors in the kidney and bone. PTH has a plasma half-life of 4 minutes.

Effects of PTH

Bone	Binds to osteoblasts which signal to osteoclasts to cause resorption of bone and release calcium.
Kidney	Active reabsorption of calcium and magnesium from the distal convoluted tubule. Decreases reabsorption of phosphate.
Intestine via kidney	Increases intestinal calcium absorption by increasing activated vitamin D. Activated vitamin D increases calcium absorption.

Glucagon

Glucagon, the hormonal antagonist to insulin, is released from the alpha cells of the Islets of Langerhans in the pancreas. It will result in an increased plasma glucose level.

Stimulation	Inhibition
Decreased plasma glucose	Somatostatin
Increased catecholamines	Insulin
Increased plasma amino acids	Increased free fatty acids and keto acids
Sympathetic nervous system	Increased urea
Acetylcholine	
Cholecystokinin	

Gastrointestinal Secretions

Up to 7 litres of gastrointestinal secretions enter the lumen of the GI tract in a 24-hour period. The absorptive function of the small bowel is such that by the time a formed stool is created, it will contain, on average 200ml water.
The common secretions together with their approximate volumes are demonstrated below:

Origin of secretion	Volume in ml / 24 hour period	Na^+ mmol/L	K^+ mmol/L	Cl^- mmol/L	HCO_3
Salivary glands	1500*	10	26	10	30
Stomach	1500	60	10	130	
Duodenum	100-2000	140	80	80	
Pancreas	1000	140	5	70	115
Bile	50-800	145	5	100	35
Jejunum/ileum	3000	140	10	104	30
Colon	100	60	30	40	

**Submandibular glands produce 800-100 ml per day*

The regulation of these secretions is dependent upon location. In the salivary glands a complex interaction of flow rate governed by the autonomic nervous system. The exact composition of sodium and potassium is regulated by aldosterone. In the stomach hormones such as gastrin play a role and feedback is both endocrine and neurologically mediated (vagus). In the duodenum CCK is released in response to duodenal distension and this causes contraction of the gallbladder and release of bile.

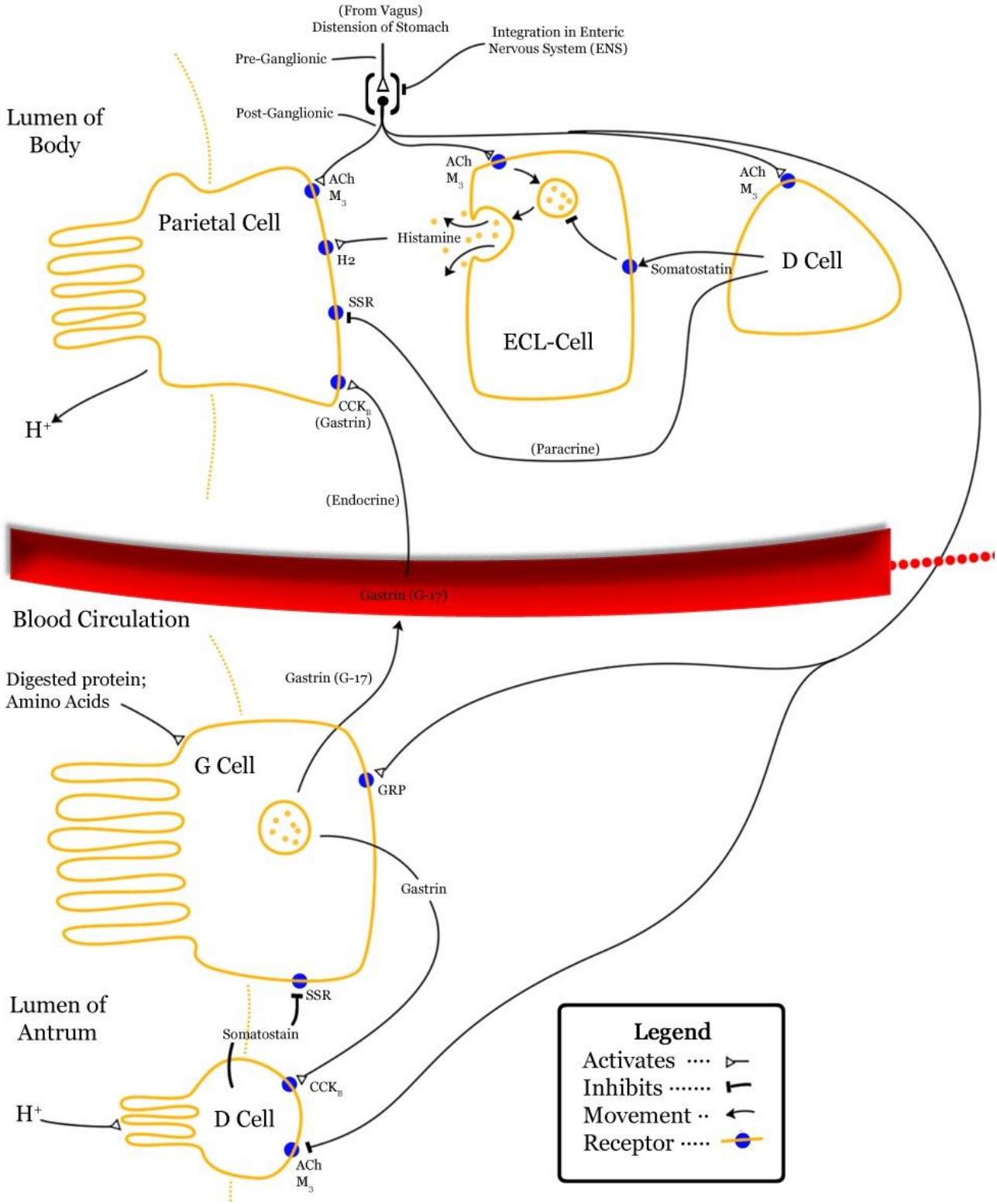
Pancreatic secretions are affected by somatostatin. The secretions in the small bowel are affected by the osmolality of the lumenal contents. This is in part due to the tightness of cellular junctions and in this regard the jejunum is more permeable than the ileum. The practical implication of this is that if an individual has an extensive intestinal resection and a high output, proximally sited stoma then administration of hypotonic rather than isotonic solutions will result in worsening of electrolyte disturbances as electrolyte rich secretions will enter the jejunum.

In some individuals a colectomy or similar procedure results in formation of an end or loop ileostomy. Ileostomies typically lose between 500 and 1000ml over a 24-hour period and patients with high output ileostomies can rapidly become dehydrated. Ileostomy effluent typically **contains 126mmol/L of sodium** and 22mmol/L of potassium. Knowledge of this fluid composition should guide fluid prescribing in replacing losses.

Gastric Secretions

Gastric acid

- Is produced by the parietal cells in the stomach
- pH of gastric acid is around 2 with acidity being maintained by the H^+/K^+ ATP ase pump. As part of the process bicarbonate ions will be secreted into the surrounding vessels.
- Sodium and chloride ions are actively secreted from the parietal cell into the canaliculus. This sets up a negative potential across the membrane and as a result sodium and potassium ions diffuse across into the canaliculus.
- Carbonic anhydrase forms carbonic acid which dissociates and the hydrogen ions formed by dissociation leave the cell via the H^+/K^+ antiporter pump. At the same time sodium ions are actively absorbed. This leaves hydrogen and chloride ions in the canaliculus these mix and are secreted into the lumen of the oxyntic gland.



Phases of gastric acid secretion

1. Cephalic phase (smell / taste of food)

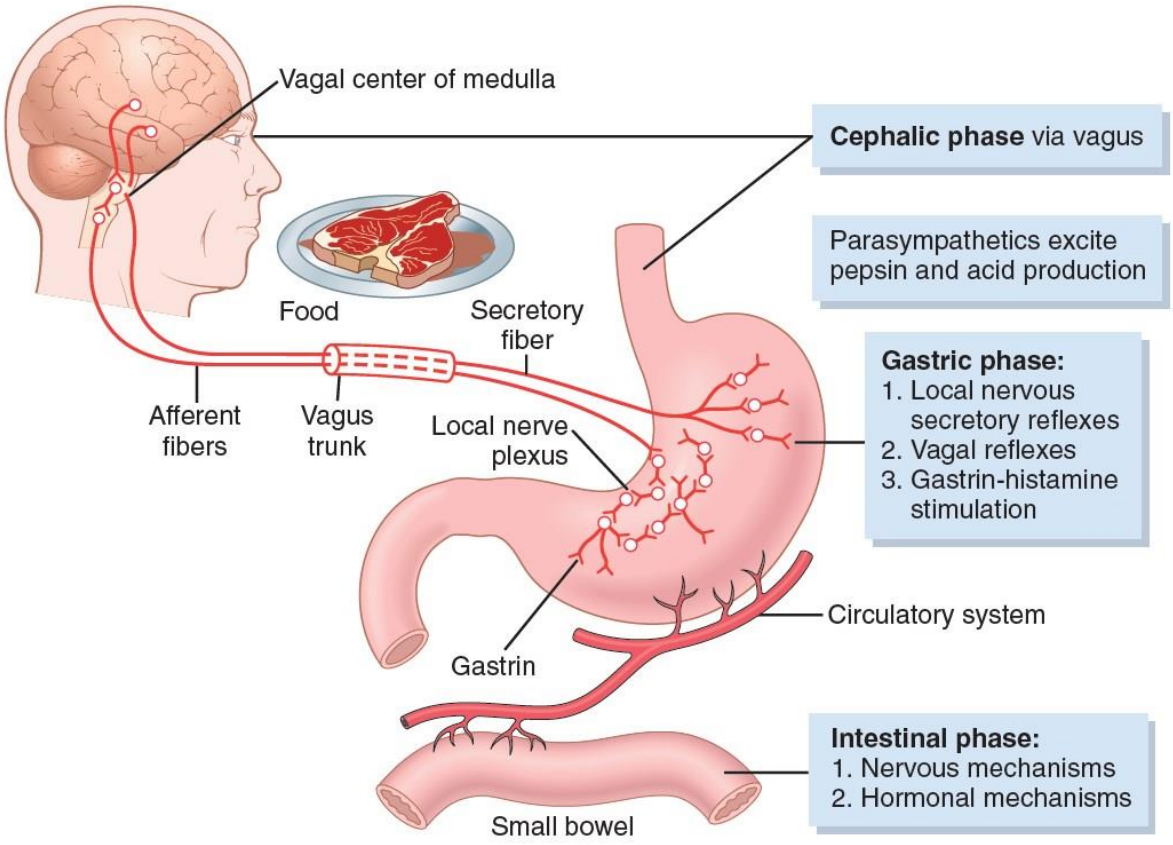
- 30% acid produced
- Vagal cholinergic stimulation causing secretion of HCL and gastrin release from G cells

2. Gastric phase (distension of stomach)

- 60% acid produced
- Stomach distension/low H^+/peptides causes Gastrin release

3. Intestinal phase (food in duodenum)

- 10% acid produced
- High acidity/distension/hypertonic solutions in the duodenum inhibits gastric acid secretion via enterogastrones (CCK, secretin) and neural reflexes.



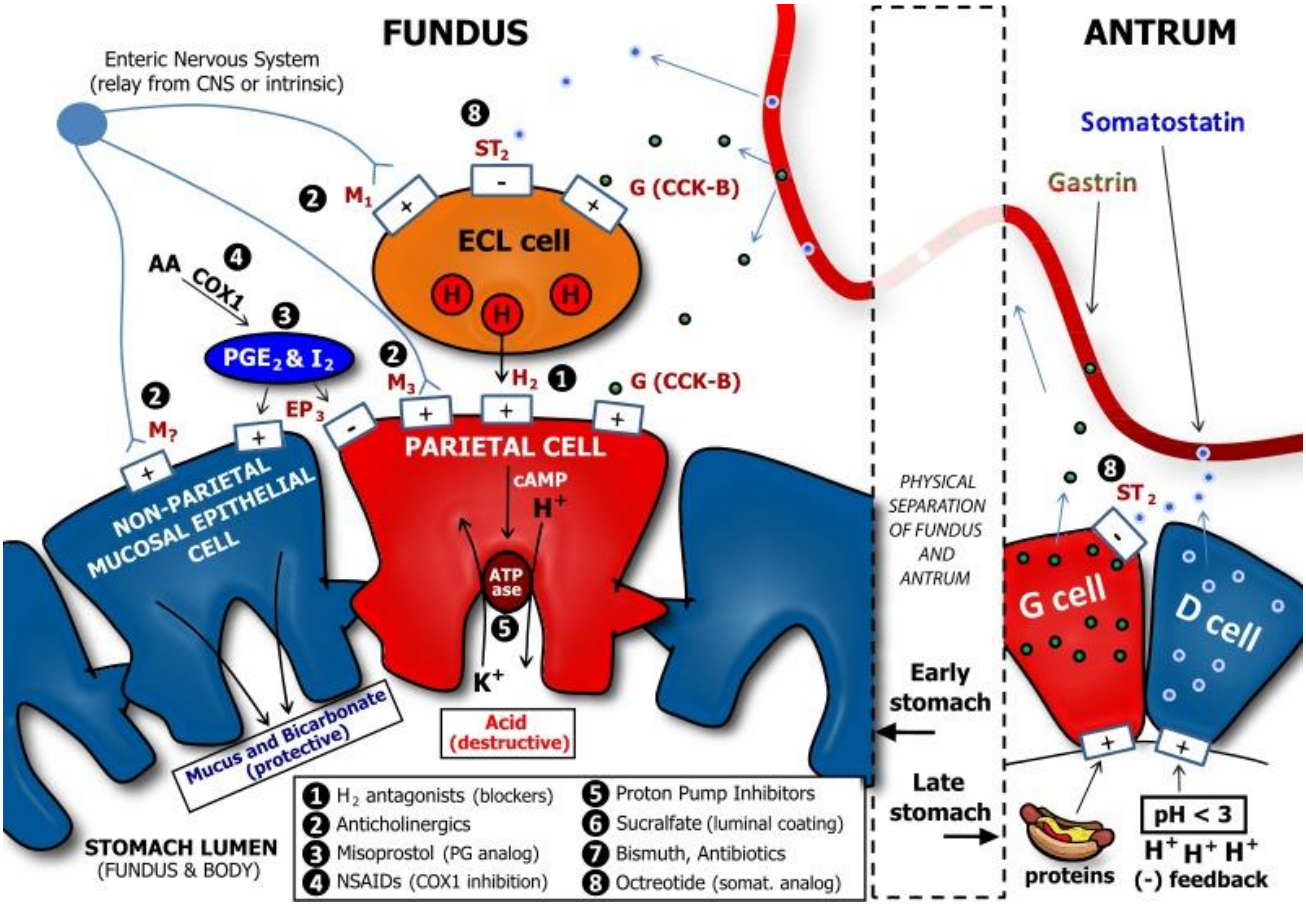
Factors increasing production include:

- Vagal nerve stimulation
- Gastrin release
- Histamine release (indirectly following gastrin release) from enterochromaffin like cells

Factors decreasing production include:

- Somatostatin (inhibits histamine release)
- Cholecystokinin
- Secretin

Parietal cells: secrete HCl, Ca, Na, Mg and intrinsic factor
Chief cells: secrete pepsinogen 'Chief of PEPSI Cola'
Surface mucosal cells: secrete mucus and bicarbonate



Name	Source	Stimulus	Actions
Gastrin	G cells in antrum of the stomach	Distension of stomach, extrinsic nerves Inhibited by: low antral pH, somatostatin	Increase HCL, pepsinogen and IF secretion, increases gastric motility, trophic effect on gastric mucosa
CCK	I cells in upper small intestine	Partially digested proteins and triglycerides	Increases secretion of enzyme-rich fluid from pancreas, contraction of gallbladder and relaxation of sphincter of Oddi, decreases gastric emptying, trophic effect on pancreatic acinar cells, induces satiety
Secretin	S cells in upper **small intestine**	Acidic chyme, fatty acids	Increases secretion of bicarbonate-rich fluid from pancreas and hepatic duct cells, decreases gastric acid secretion, trophic effect on pancreatic acinar cells
VIP	Small intestine, pancreas	Neural	Stimulates secretion by pancreas and intestines, inhibits acid and pepsinogen secretion
Somatostatin	D cells in the **pancreas** and stomach	Fat, bile salts and glucose in the intestinal lumen	Decreases acid and pepsin secretion, decreases gastrin secretion, decreases pancreatic enzyme secretion, decreases insulin and glucagon secretion inhibits trophic effects of gastrin, stimulates gastric mucous production

Peristalsis

- Circular smooth muscle contracts behind the food bolus and longitudinal smooth muscle propels the food through the oesophagus
- Primary peristalsis spontaneously moves the food from the oesophagus into the stomach (9 seconds)
- Secondary peristalsis occurs when food, which doesn't enter the stomach, stimulates stretch receptors to cause peristalsis
- In the small intestine each peristalsis waves slows to a few seconds and causes mixture of chyme
- In the colon three main types of peristaltic activity are recognised (see below)

Colonic peristalsis

Segmentation contractions	Localised contractions in which the bolus is subjected to local forces to maximise mucosal absorption
Antiperistaltic contractions towards ileum	Localised reverse peristaltic waves to slow entry into colon and maximise absorption
Mass movements	Waves migratory peristaltic waves along the entire colon to empty the organ prior to the next ingestion of food bolus

Pancreas Endocrine Physiology

Hormones released from the islets of Langerhans

Beta cells	Insulin (70% of total secretions)
Alpha cells	Glucagon
Delta cells	Somatostatin
F cells	Pancreatic polypeptide

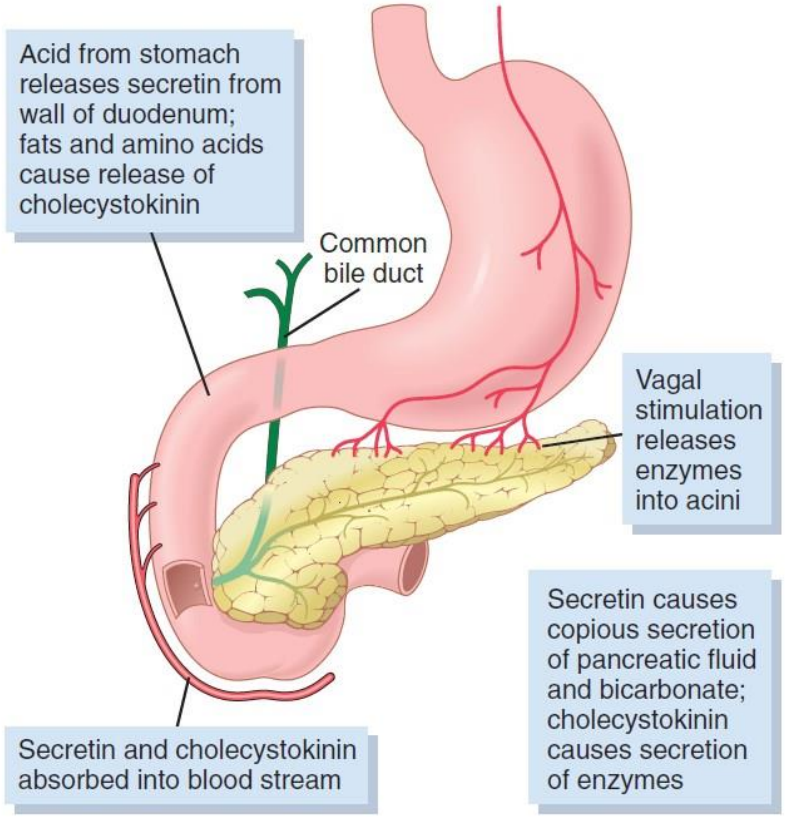
Pancreas Exocrine Physiology

Composition of pancreatic secretions

Pancreatic secretions are usually 1000-1500ml per 24 hours and have a pH of 8.

Secretion	Source	Substances secreted
Enzymic	Acinar cells	Trypsinogen Procarboxylase Amylase Elastase
Aqueous	Ductal and Centroacinar cells	Sodium Bicarbonate Water Potassium Chloride

NB: Sodium and potassium reflect their plasma levels; chloride and bicarbonate vary with flow rate



Regulation

The cephalic and gastric phases (neuronal and physical) are less important in regulating the pancreatic secretions. The effect of digested material in the small bowel stimulates CCK release and ACh which stimulate acinar and ductal cells. Of these CCK is the most potent stimulus. In the case of the ductal cells these are potently stimulated by secretin which is released by the S cells of the duodenum. This results in an increase in bicarbonate.

Enzyme activation

Trypsinogen is converted via enterokinase to active trypsin in the duodenum. Trypsin then activates the other inactive enzymes

Renal Physiology

Overview

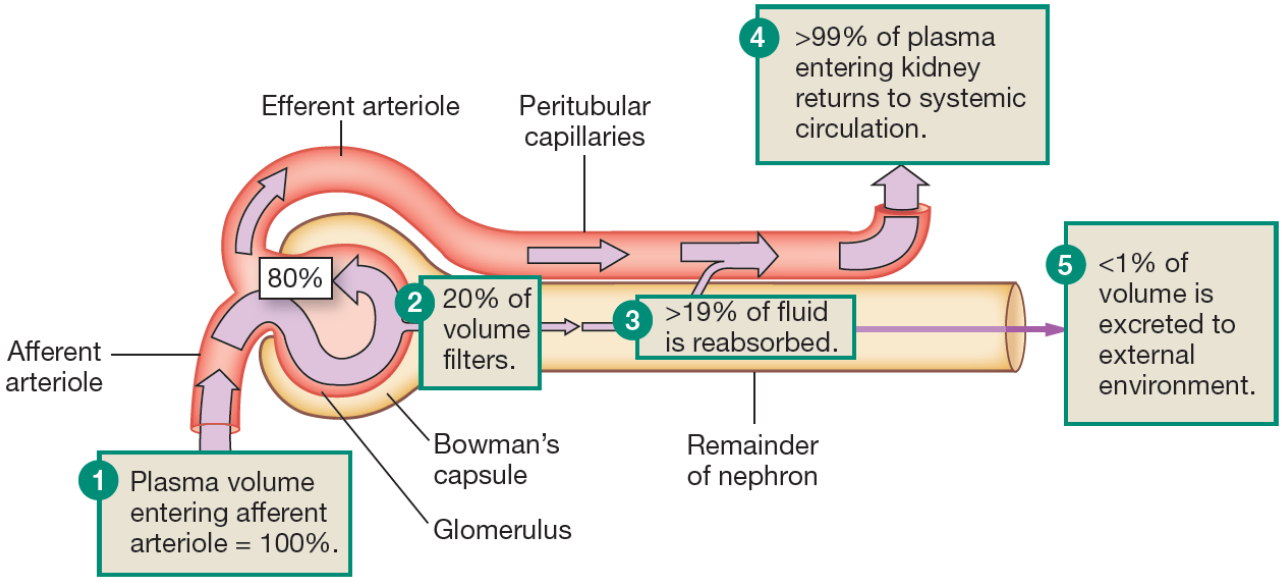
- Each nephron is supplied with blood from an afferent arteriole that opens onto the glomerular capillary bed.
- Blood then flows to an efferent arteriole, supplying the peritubular capillaries and medullary vasa recta.
- The kidney receives up to 25% of resting cardiac output.

Control of blood flow

- The kidney is able to auto regulate its blood flow between systolic pressures of 80- 180mmHg so there is little variation in renal blood flow.
- This is achieved by myogenic control of arteriolar tone, both sympathetic input and hormonal signals (e.g. renin) are responsible.

Glomerular structure and function

- Blood inside the glomerulus has considerable hydrostatic pressure.
- The basement membrane has pores that will allow free diffusion of smaller solutes, larger negatively charged molecules such as albumin are unable to cross.
- The glomerular filtration rate (GFR) is equal to the concentration of a solute in the urine, times the volume of urine produced per minute, divided by the plasma concentration (assuming that the solute is freely diffused e.g. inulin).
- In clinical practice creatinine is used because it is subjected to very little proximal tubular secretion.
- Although subject to variability, the typical GFR is 125ml per minute.
- Glomerular filtration rate = Total volume of plasma per unit time leaving the capillaries and entering the bowman's capsule
- Renal clearance = volume plasma from which a substance is removed per minute by the kidneys



Only 20% of the plasma that passes through the glomerulus is filtered. Less than 1% of filtered fluid is eventually excreted.

Substances used to measure GFR have the following features:

- Inert
- **Free filtration** from the plasma at the glomerulus (not protein bound)
- **Not absorbed nor secreted** at the tubules
- Plasma concentration constant during urine collection

Examples: inulin, creatinine

$$GFR = \frac{\text{urine concentration (mmol/l) x urine volume (ml/min)}}{\text{plasma concentration (mmol/l)}}$$

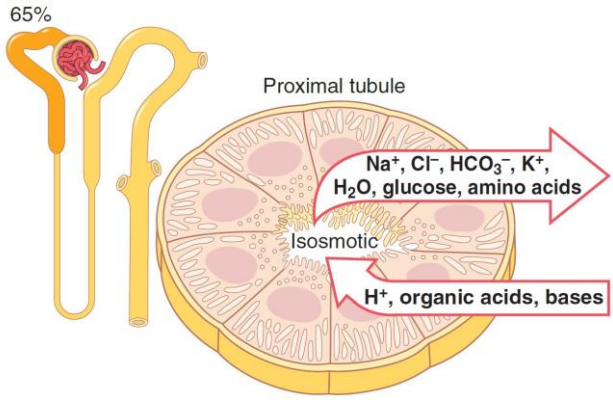
- The clearance of a substance is dependent not only on its diffusivity across the basement membrane but also subsequent tubular secretion and / or reabsorption.
- So glucose which is freely filtered across the basement membrane is usually reabsorbed from tubules giving a clearance of zero.

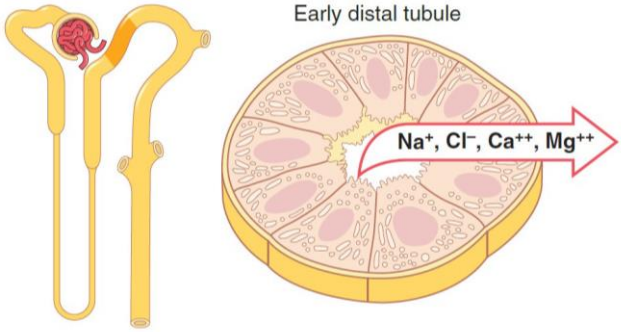
Tubular function

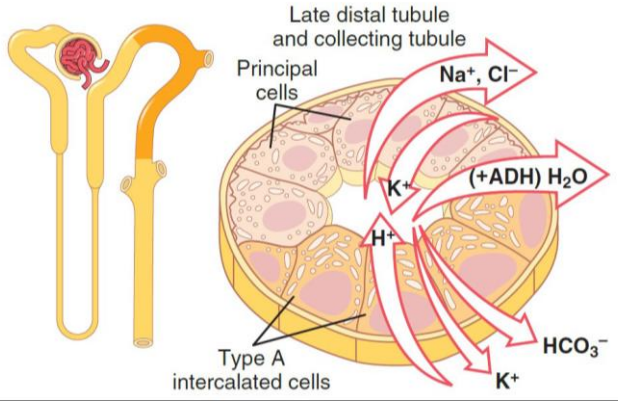
- Reabsorption and secretion of substances occurs in the tubules.
- In the proximal tubule substrates such as glucose, amino acids and phosphate are co-transported with sodium across the semi permeable membrane.
- Up to two thirds of filtered water is reabsorbed in the proximal tubules.
- This will lead to increase in urea concentration in the distal tubule allowing for its increased diffusion.
- Substances to be secreted into the tubules are taken up from the peritubular blood by tubular cells.
- Solutes such as paraaminohippuric acid are cleared with a single passage through the kidneys and this is why it is used to measure renal plasma flow. Ions such as calcium and phosphate will have a tubular reabsorption that is influenced by plasma PTH levels.
- Potassium may be both secreted and re-absorbed and is co-exchanged with sodium.

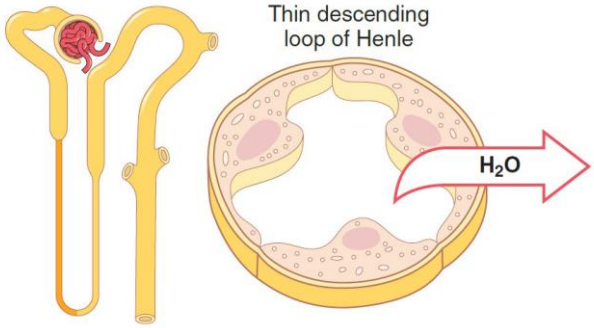
Loop of Henle

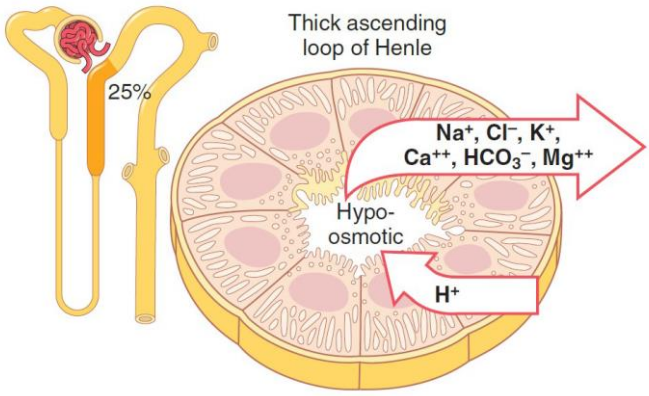
- Approximately 60 litres of water containing 9000mmol sodium enters the descending limb of the loop of Henle in 24 hours.
- Loops from the juxtamedullary nephrons run deep into the medulla.
- The osmolarity of fluid changes and is greatest at the tip of the papilla.
- The thin ascending limb is impermeable to water, but highly permeable to sodium and chloride ions.
- This loss means that at the beginning of the thick ascending limb the fluid is hypo osmotic compared with adjacent interstitial fluid.
- In the thick ascending limb the reabsorption of sodium and chloride ions occurs by both facilitated and passive diffusion pathways.
- The loops of Henle are co-located with vasa recta, these will have similar solute compositions to the surrounding extracellular fluid so preventing the diffusion and subsequent removal of this hypertonic fluid.
- The energy dependent reabsorption of sodium and chloride in the thick ascending limb helps to maintain this osmotic gradient.

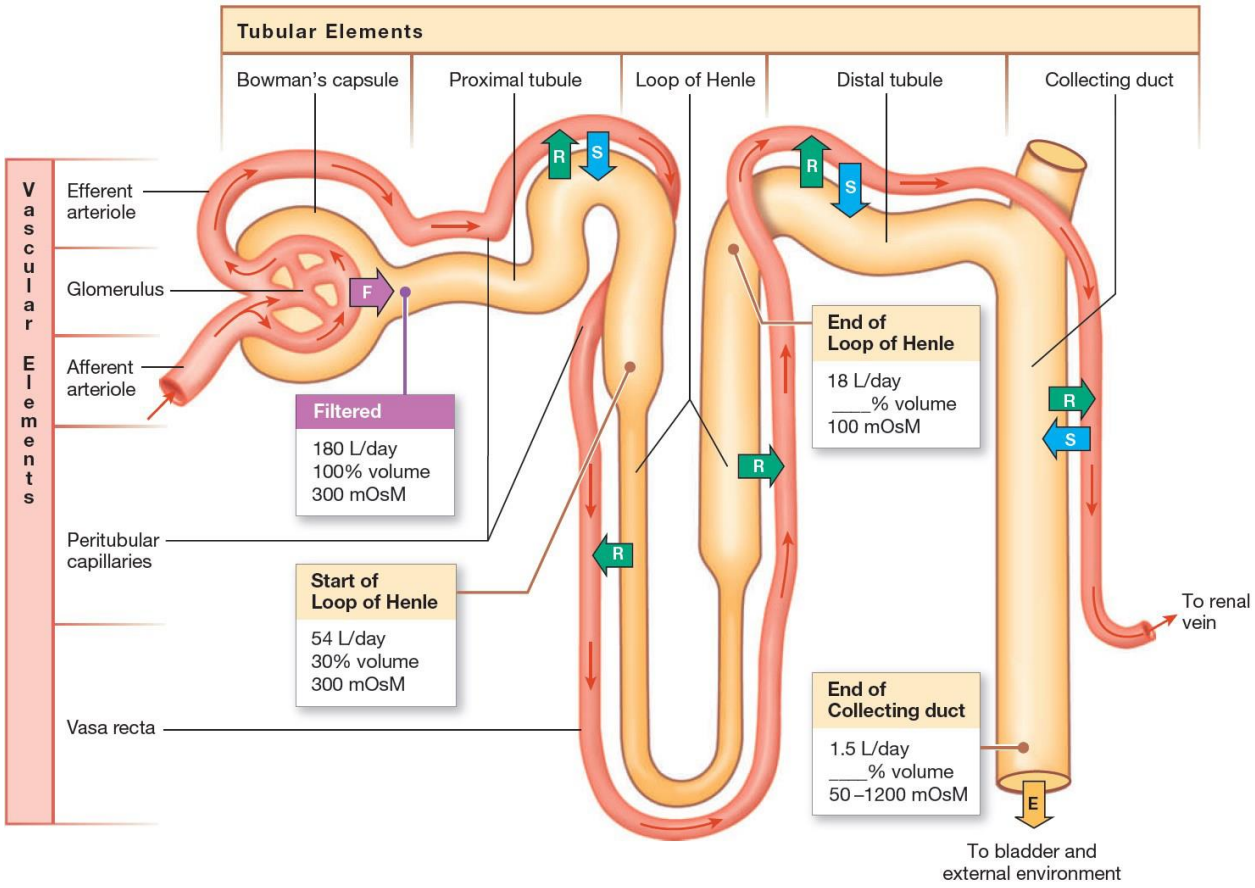












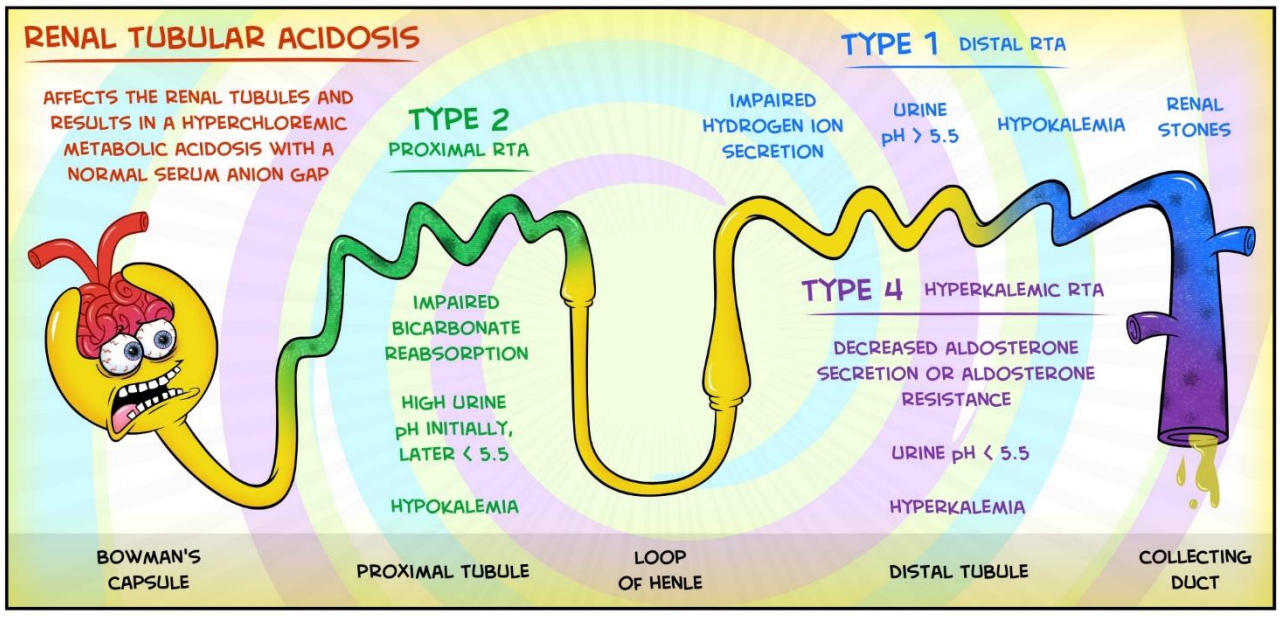
Acute Renal Failure: Pre Renal Failure Vs. Acute Tubular Necrosis

Prerenal uraemia - kidneys retain sodium to preserve volume

	Pre-renal uraemia	Acute tubular necrosis
Urine sodium	< 20 mmol/L	> 30 mmol/L
Fractional sodium excretion*	< 1%	> 1%
Fractional urea excretion**	< 35%	>35%
Urine:plasma osmolality	> 1.5	< 1.1
Urine:plasma urea	> 10:1	< 8:1
Specific gravity	> 1020	< 1010
Urine	'bland' sediment	brown granular casts
Response to fluid challenge	Yes	No

**fractional sodium excretion = (urine sodium/plasma sodium) / (urine creatinine/plasma creatinine) x 100*

***fractional urea excretion = (urine urea /blood urea) / (urine creatinine/plasma creatinine) x 100*



Acute Renal Failure Causes

- Final pathway is tubular cell death.
- Renal medulla is a relatively hypoxic environment making it susceptible to renal tubular hypoxia.
- Renovascular autoregulation maintains renal blood flow across a range of arterial pressures.
- Estimates of GFR are best indices of level of renal function. Useful clinical estimates can be obtained by considering serum creatinine, age, race, gender and body size. eGFR calculations such as the Cockcroft and Gault equation are less reliable in populations with high GFR's.
- Nephrotoxic stimuli such as aminoglycosides and radiological contrast media induce apoptosis. Myoglobinuria and hemolysis result in necrosis. Overlap exists and proinflammatory cytokines play and important role in potentiating ongoing damage.
- Post-operative renal failure is more likely to occur in patients who are elderly, have peripheral vascular disease, high BMI, have COPD, receive vasopressors, are on nephrotoxic medication or undergo emergency surgery.
- Avoiding hypotension will reduce risk of renal tubular damage.
- There is no evidence that administration of ACEI or dopamine reduces the incidence of post-operative renal failure.

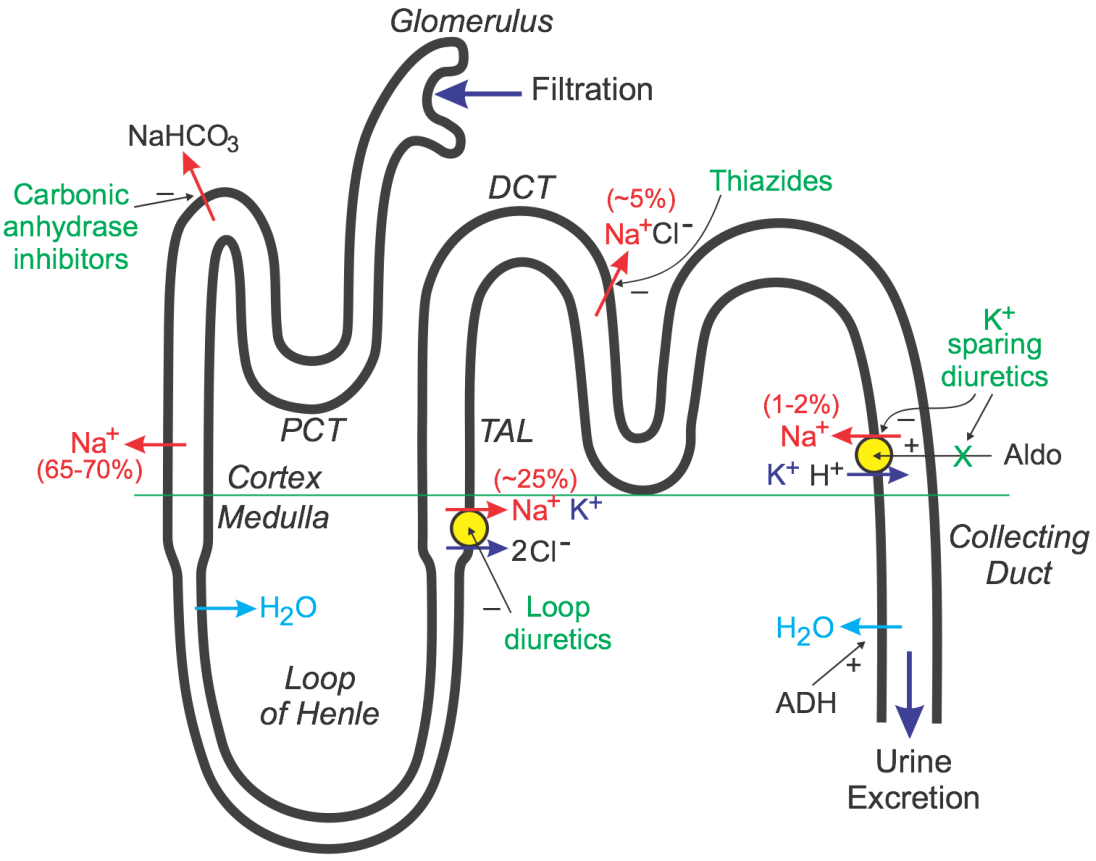
Pre-renal	Renal	Post-renal
• **Hge** • **Dehydration** • **Burns** • **Sepsis**	• NSAIDs • ACEI • Aminoglycosides • Contrast	• Ureteric & lower urinary tract obstruction

Diuretic Agents

The diuretic drugs are divided into three major classes, which are distinguished according to the site at which they impair sodium reabsorption: loop diuretics in the thick ascending loop of Henle, thiazide type diuretics in the distal tubule and connecting segment; and potassium sparing diuretics in the aldosterone - sensitive principal cells in the cortical collecting tubule.

In the kidney, sodium is reabsorbed through Na^+/ K^+ ATPase pumps located on the basolateral membrane. These pumps return reabsorbed sodium to the circulation and maintain low intracellular sodium levels. This latter effect ensures a constant concentration gradient.

Site of action	Diuretic	Carrier or channel inhibited	% of filtered sodium excreted
Ascending limb of loop of Henle	Frusemide	Na^+/K^+ $2Cl^-$ carrier	Up to **25%**
Distal tubule and connecting segment	Thiazides	Na^+ Cl^- carrier	Between 3 and 5%
Cortical collecting tubule	Spironolactone	Na^+/K^+ ATPase pump	Between 1 and 2%



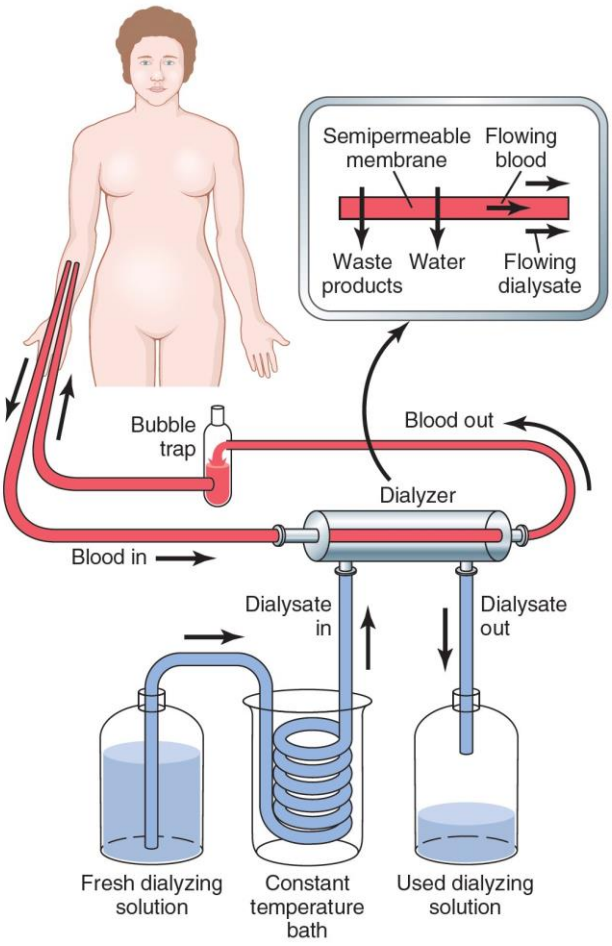
Renal Replacement Therapy

Indications *(see NICE NG107)*

- Persistent hyperkalemia (K^+ > 6 mmol/L)
- Metabolic acidosis (pH >7.2)
- Uncontrollable fluid overload
- Urea > 30 mmol/L
- eGFR 5-7 ml/min/1.73m^2
- Complicated uremia e.g. encephalopathy

Continuous Venous Hemodiafiltration	Intermittent Hemodialysis	Chronic Ambulatory Peritoneal Dialysis
• In unstable, critically ill patients • No need for fistula • e.g. ARF due to sepsis, ATN due to long supra-renal clamp	• The most efficient method in stable patients • Large amount of fluid can be removed	*Ideal for patients with* • Bleeding tendency • Needle phobia • Poor cardiac function who cannot tolerate hypotension • Busy job makes it the best option

Obesity & risk of abdominal adhesions make peritoneal dialysis less performed



Principles of dialysis with an artificial kidney

Syndrome of Inappropriate Antidiuretic Hormone (SIADH): Causes

Malignancy

- Especially small cell lung cancer
- Also: pancreas, prostate

Neurological

- Stroke
- Subarachnoid haemorrhage
- Subdural haemorrhage
- Meningitis/encephalitis/abscess

Infections

- Tuberculosis
- Pneumonia

Drugs

- Sulfonylureas
- SSRIs, tricyclics
- Carbamazepine
- Vincristine
- Cyclophosphamide

Other causes

- Positive end-expiratory pressure (PEEP)
- Porphyrias

Renin

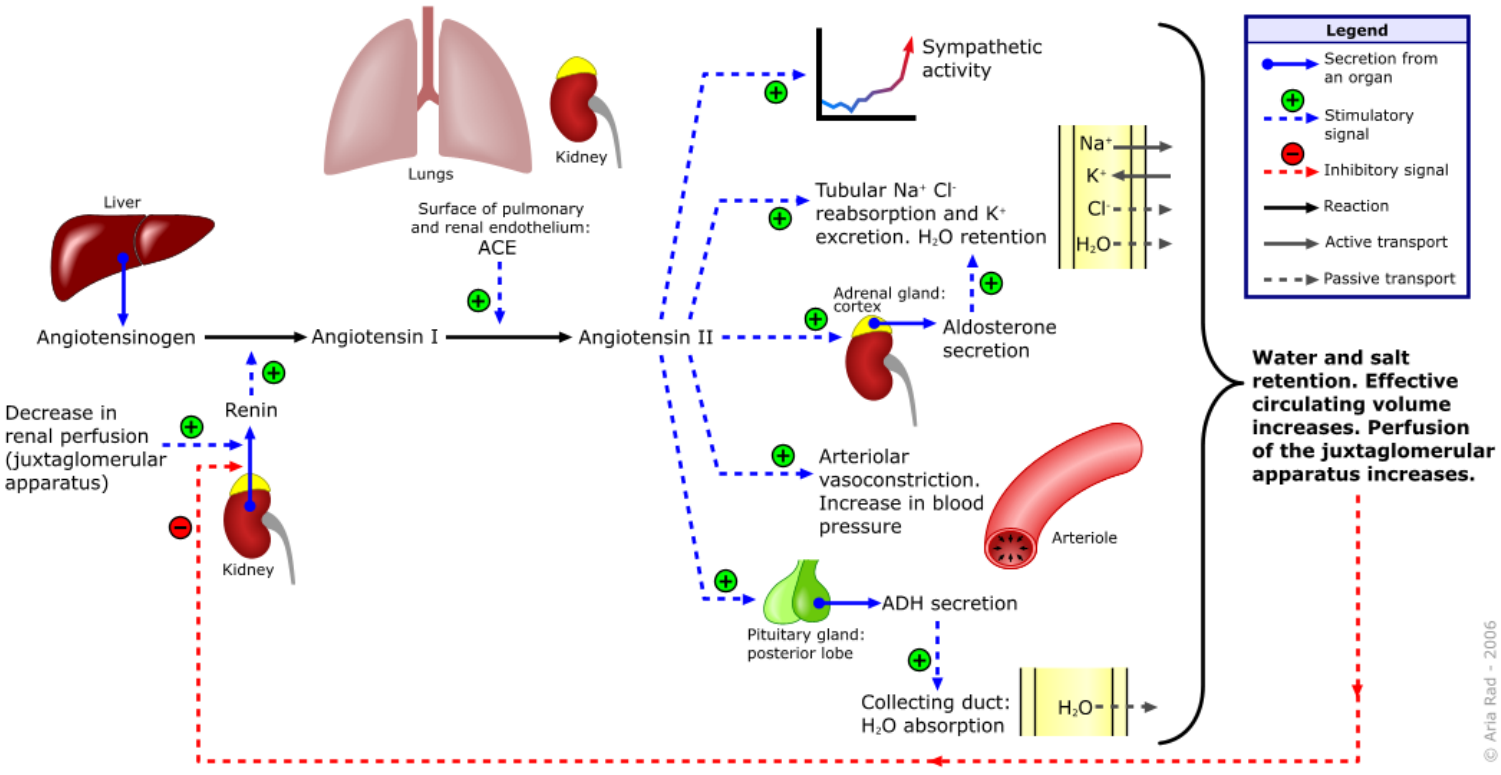
Renin is secreted by juxtaglomerular cells and hydrolyses angiotensinogen to produce angiotensin I

Factors stimulating renin secretion

- Hypotension causing reduced renal perfusion
- Hyponatraemia
- Sympathetic nerve stimulation
- Catecholamines
- Erect posture

Factors reducing renin secretion

- Drugs: beta-blockers, NSAIDs



Renin-Angiotensin-Aldosterone System

Adrenal cortex (mnemonics **GFR – ACD** / *"salt, sugar, sex"*)

- Zona **g**lomerulosa (on outside): mineralocorticoids, mainly **a**ldosterone
- Zona **f**asciculata (middle): glucocorticoids, mainly **c**ortisol
- Zona **r**eticularis (on inside): androgens, mainly **d**ehydroepiandrosterone (DHEA)

Renin

- Released by JGA cells in kidney in response to reduced renal perfusion, low sodium
- Hydrolyses angiotensinogen to form angiotensin I

Factors stimulating renin secretion

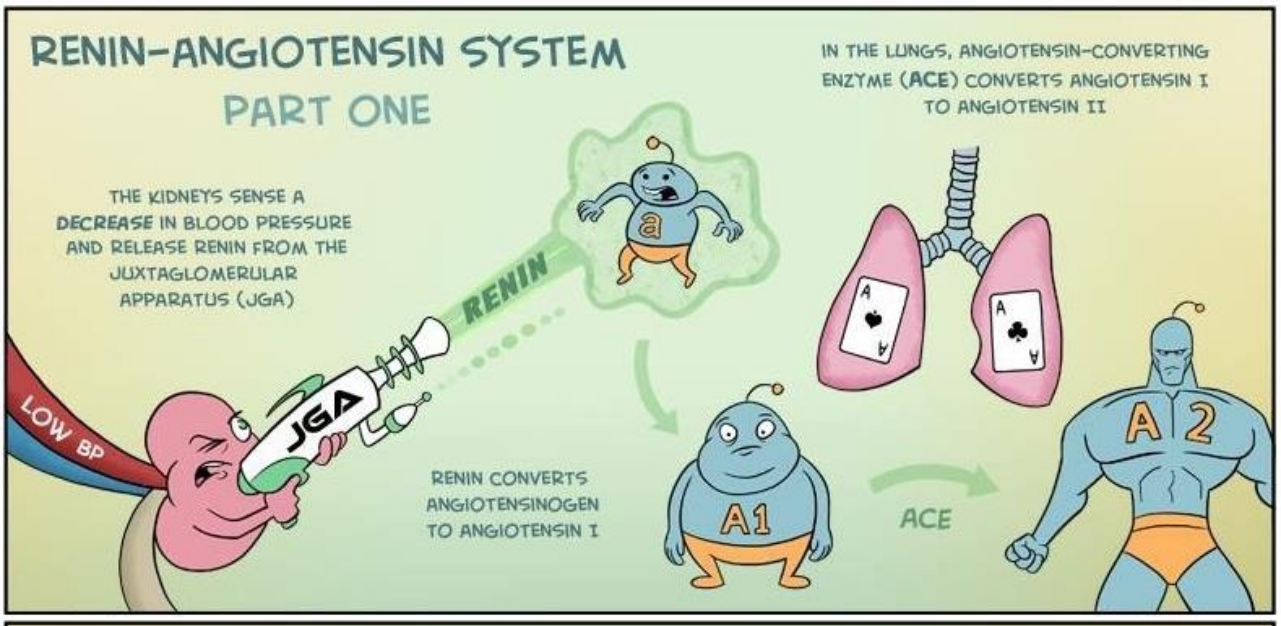
- Low BP
- Hyponatraemia
- Sympathetic nerve stimulation
- Catecholamines
- Erect posture

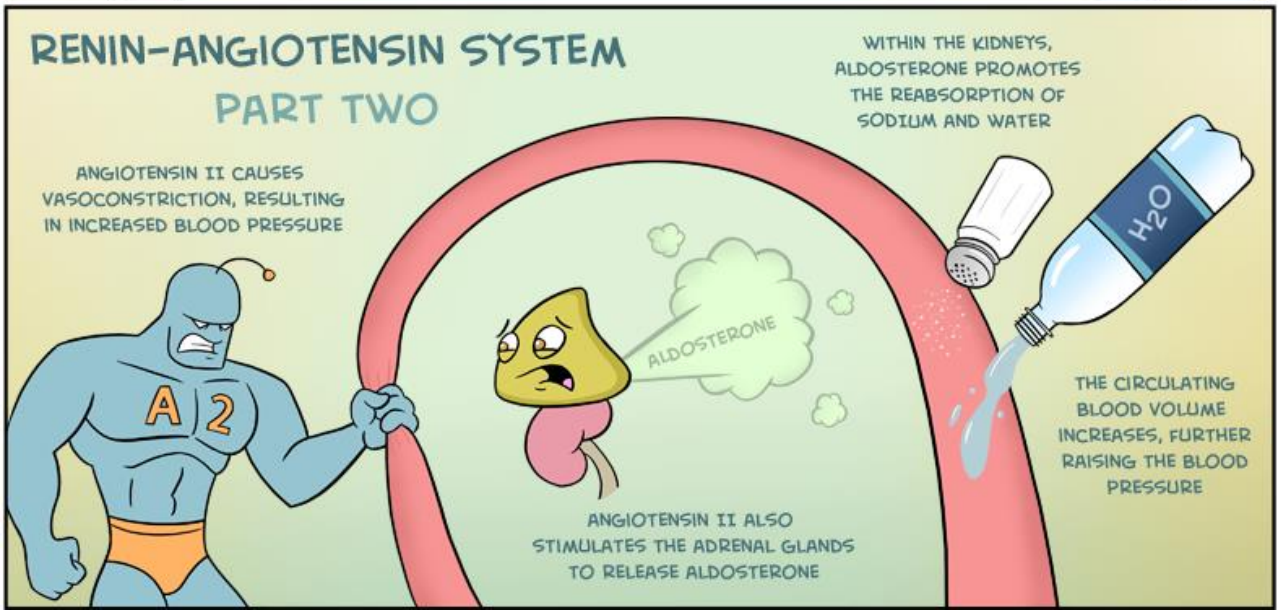
Angiotensin

- ACE in lung converts angiotensin I → angiotensin II
- Vasoconstriction leads to raised BP
- Stimulates thirst
- Stimulates aldosterone and ADH release

Aldosterone

- Released by the zona glomerulosa in response to raised angiotensin II, potassium, and ACTH levels
- Causes retention of Na^+ in exchange for K^+/H^+ in distal tubule





Phases of Wound Healing

Phase	Key features	Cells	Timeframe
Haemostasis	• Vasospasm in adjacent vessels • Platelet plug formation and generation of fibrin rich clot	Erythrocytes and platelets	Seconds / Minutes
Inflammation	• Neutrophils migrate into wound (function impaired in diabetes). • Growth factors released, including basic fibroblast growth factor and vascular endothelial growth factor. • Fibroblasts replicate within the adjacent matrix and migrate into wound. • Macrophages and fibroblasts couple matrix regeneration and clot substitution.	Neutrophils, fibroblasts and macrophages	Days
Regeneration	• Platelet derived growth factor and transformation growth factors stimulate fibroblasts and epithelial cells. • Fibroblasts produce a collagen network. • Angiogenesis occurs and wound resembles granulation tissue.	Fibroblasts, endothelial cells, macrophages	Weeks
Remodelling	• Longest phase of the healing process and may last up to one year (or longer). • During this phase, fibroblasts become differentiated (myofibroblasts) and these facilitate wound contraction. • Collagen fibres are remodelled. • Microvessels regress leaving a pale scar.	Myofibroblasts	6 weeks to 1 year

Response to Surgery

Sympathetic nervous system

- Noradrenaline from sympathetic nerves and adrenaline from adrenal medulla
- Blood diverted from skin and visceral organs; bronchodilatation, reduced intestinal motility, increased glucagon and glycogenolysis, insulin reduced
- Heart rate and myocardial contractility are increased

Acute phase response

- TNF-α, IL-1, IL-2, IL-6, interferon and prostaglandins are released
- Excess cytokines may cause SIRS
- Cytokines increase the release of acute phase proteins

Endocrine response

- Hypothalamus, pituitary, adrenal axis
- Increases ACTH and cortisol production:

increases protein breakdown
increases blood glucose levels

- Aldosterone increases sodium re-absorption
- Vasopressin increases water re-absorption and causes vasoconstriction

Vascular endothelium

- Nitric oxide produces vasodilatation
- Platelet activating factor enhances the cytokine response
- Prostaglandins produce vasodilatation and induce platelet aggregation

Stress Response: Endocrine and Metabolic Changes

- Surgery precipitates hormonal and metabolic changes causing the stress response.
- Stress response is associated with: substrate mobilization, muscle protein loss, sodium and water retention, suppression of anabolic hormone secretion, activation of the sympathetic nervous system, immunological and haematological changes.
- The hypothalamic-pituitary axis and the sympathetic nervous systems are activated and there is a failure of the normal feedback mechanisms of control of hormone secretion.

A summary of the hormonal changes associated with the stress response:

Increased	Decreased	No Change
Growth hormone	Insulin	Thyroid stimulating hormone
Cortisol	Testosterone	Luteinizing hormone
Renin	Oestrogen	Follicle stimulating hormone
Adrenocorticotrophic hormone (ACTH)		
Aldosterone		
Prolactin		
Antidiuretic hormone		
Glucagon		

Sympathetic nervous system

- Stimulates catecholamine release
- Causes tachycardia and hypertension

Pituitary gland

- ACTH and growth hormone (GH) is stimulated by hypothalamic releasing factors, corticotrophin releasing factor (CRF) and somatotrophin (or growth hormone releasing factor)
- Perioperative increased prolactin secretion occurs by release of inhibitory control
- Secretion of thyroid stimulating hormone (TSH), luteinizing hormone (LH) and follicle stimulating hormone (FSH) does not change significantly
- ACTH stimulates cortisol production within a few minutes of the start of surgery. More ACTH is produced than needed to produce a maximum adrenocortical response.

Cortisol

- Significant increases within 4-6 hours of surgery (>1000 nmol litre^{-1}).
- The usual negative feedback mechanism fails and concentrations of ACTH and cortisol remain persistently increased.
- The magnitude and duration of the increase correlate with the severity of stress and the response is not abolished by the administration of corticosteroids.
- The metabolic effects of cortisol are enhanced:
    - Skeletal muscle protein breakdown to provide gluconeogenic precursors and amino acids for protein synthesis in the liver
    - Stimulation of lipolysis
    - 'Anti-insulin effect'
    - Mineralocorticoid effects
    - Anti-inflammatory effects

Growth hormone

- Increased secretion after surgery has a minor role
- Most important for preventing muscle protein breakdown and promote tissue repair by insulin growth factors

Alpha Endorphin

- Increased

Antidiuretic hormone

- An important vasopressor and enhances haemostasis
- Renin is released causing the conversion of angiotensinogen to angiotensin I
- Angiotensin II formed by ACE on angiotensin 1, which causes the secretion of aldosterone from the adrenal cortex. This increases sodium reabsorption at the distal convoluted tubule

Insulin

- Release inhibited by stress
- Occurs via the inhibition of the beta cells in the pancreas by the α2-adrenergic inhibitory effects of catecholamines
- Insulin resistance by target cells occurs later
- The perioperative period is characterized by a state of functional insulin deficiency

Stimulation of insulin release:

- Glucose
- Amino acid
- Vagal cholinergic
- Secretin/Gastrin/CCK
- Fatty acids
- Beta adrenergic drugs

Inhibition of Insulin release

- Alpha adrenergic drugs
- Beta blockers
- Sympathetic nerves

Thyroxine (T4) and tri-iodothyronine (T3)

- Circulating concentrations are inversely correlated with sympathetic activity and after surgery there is a reduction in thyroid hormone production, which normalises over a few days.

Metabolic effect of endocrine response

Carbohydrate metabolism

- Hyperglycaemia is a main feature of the metabolic response to surgery
- Due to increase in glucose production and a reduction in glucose utilization
- Catecholamines and cortisol promote glycogenolysis and gluconeogenesis
- Initial failure of insulin secretion followed by insulin resistance affects the normal responses
- The proportion of the hyperglycaemic response reflects the severity of surgery
- Hyperglycaemia impairs wound healing and increase infection rates

Protein metabolism

- Initially there is inhibition of protein anabolism, followed later, if the stress response is severe, by enhanced catabolism
- The amount of protein degradation is influenced by the type of surgery and also by the nutritional status of the patient
- Mainly skeletal muscle protein is affected
- The amino acids released form acute phase proteins (fibrinogen, C reactive protein, complement proteins, a2-macroglobulin, amyloid A and ceruloplasmin) and are used for gluconeogenesis
- Nutritional support has little effect on preventing catabolism

Lipid metabolism

- Increased catecholamine, cortisol and glucagon secretion, and insulin deficiency, promotes lipolysis and ketone body production.

Salt and water metabolism

- ADH causes water retention, concentrated urine, and potassium loss and may continue for 3 to 5 days after surgery
- Renin causes sodium and water retention

Cytokines

- Glycoproteins
- Interleukins (IL) 1 to 17, interferons, and tumour necrosis factor
- Synthesized by activated macrophages, fibroblasts, endothelial and glial cells in response to tissue injury from surgery or trauma
- IL-6 main cytokine associated with surgery. Peak 12 to 24 h after surgery and increase by the degree of tissue damage Other effects of cytokines include fever, granulocytosis, haemostasis, tissue damage limitation and promotion of healing.

Modifying the response

- Opioids suppress hypothalamic and pituitary hormone secretion
- At high doses the hormonal response to pelvic and abdominal surgery is abolished. However, such doses prolong recovery and increase the need for postoperative ventilatory support
- Spinal anaesthesia can reduce the glucose, ACTH, cortisol, GH and epinephrine changes, although cytokine responses are unaltered
- Cytokine release is reduced in less invasive surgery
- Nutrition prevents the adverse effects of the stress response. Enteral feeding improves recovery
- Growth hormone and anabolic steroids may improve outcome
- Normothermia decreases the metabolic response

Urinary Incontinence

Involuntary passage of urine. Most cases are female (80%). It has a prevalence of 11% in those aged greater than 65 years. The commonest variants include:

- Stress urinary incontinence (50%)
- Urge incontinence (15%)
- Mixed (35%)

Males

Males may also suffer from incontinence although it is a much rarer condition in men. A number of anatomical factors contribute to this. Males have 2 powerful sphincters; one at the bladder neck and the other in the urethra. Damage to the bladder neck mechanism is a factor in causing retrograde ejaculation following prostatectomy. The short segment of urethra passing through the urogenital diaphragm consists of striated muscle fibres (the external urethral sphincter) and smooth muscle capable of more sustained contraction. It is the latter mechanism that maintains continence following prostatectomy.

Females

The sphincter complex at the level of bladder neck is poorly developed in females. As a result the external sphincter complex is functionally more important, its composition being similar to that of males. Innervation is via the pudendal nerve and the neuropathy that may accompany obstetric events may compromise this and lead to stress urinary incontinence.

Innervation

Somatic innervation to the bladder is via the pudendal, hypogastric and pelvic nerves. Autonomic nerves travel in these nerve fibres too. Bladder filling leads to detrusor relaxation (sympathetic) coupled with sphincter contraction. The parasympathetic system causes detrusor contraction and sphincter relaxation. Overall control of micturition is centrally mediated via centres in the Pons.

Stress urinary incontinence

- 50% of cases, especially in females.
- Damage (often obstetric) to the supporting structures surrounding the bladder may lead to urethral hypermobility.
- Other cases due to sphincter dysfunction, usually from neurological disorders (e.g. Pudendal neuropathy, multiple sclerosis).

Urethral mobility:
Pressure not transmitted appropriately to the urethra resulting in involuntary passage of urine during episodes of raised intra-abdominal pressure.

Sphincter dysfunction:
Sphincter fails to adapt to compress urethra resulting in involuntary passage of urine. When the sphincter completely fails there is often to continuous passage of urine.

Urge incontinence

In these patients there is sense of urgency followed by incontinence. The detrusor muscle in these patients is unstable and urodynamic investigation will demonstrate overactivity of the detrusor muscle at inappropriate times (e.g. Bladder filling). Urgency may be seen in patients with overt neurological disorders and those without. The pathophysiology is not well understood but poor central and peripheral co-ordination of the events surrounding bladder filling are the main processes.

Assessment

Careful history and examination including vaginal examination for cystocele.
Bladder diary for at least 3 days
Consider flow cystometry if unclear symptomatology or surgery considered and diagnosis is unclear.
Exclusion of other organic disease (e.g. Stones, UTI, Cancer)

Management

Conservative measures should be tried first; Stress urinary incontinence or mixed symptoms should undergo 3 months of pelvic floor exercise. Over active bladder should have 6 weeks of bladder retraining.
Drug therapy for women with overactive bladder should be offered oxybutynin (or solifenacin if elderly) if conservative measures fail.
In women with detrusor instability who fail non operative therapy a trial of sacral neuromodulation may be considered, with conversion to permanent implant if good response. Augmentation cystoplasty is an alternative but will involve long term intermittent self catheterisation.
In women with stress urinary incontinence a urethral sling type procedure may be undertaken. Where cystocele is present in association with incontinence it should be repaired particularly if it lies at the introitus.

NICE guidelines

- Initial assessment urinary incontinence should be classified as stress/urge/mixed.
- At least 3/7 bladder diary if unable to classify easily.
- Start conservative treatment before urodynamic studies if a diagnosis is obvious from the history
- Urodynamic studies if plans for surgery.
- Stress incontinence: Pelvic floor exercises 3/12, if fails consider surgery.
- Urge incontinence: Bladder training >6/52, if fails for oxybutynin (antimuscarinic drugs) then sacral nerve stimulation.
- Pelvic floor exercises offered to all women in their 1st pregnancy.

Adrenal Physiology

Adrenal medulla

The chromaffin cells of the adrenal medulla secrete the catecholamines noradrenaline and adrenaline. The medulla is innervated by the splanchnic nerves; the preganglionic sympathetic fibres secrete acetylcholine causing the chromaffin cells to secrete their contents by exocytosis.
Phaeochromocytomas are derived from these cells and will secrete both adrenaline and nor adrenaline.

Adrenal cortex

Zone	Location	Hormone Secreted
Zona glomerulosa	Outer zone	Aldosterone
Zona fasciculata	Middle zone	Glucocorticoids
Zona reticularis	Inner zone	Androgens

The glucocorticoids and aldosterone are mostly bound to plasma proteins in the circulation. Glucocorticoids are inactivated and excreted by the liver.

Vitamin Deficiency

Vitamin	Effect of deficiency
A (Retinoids)	Night blindness Epithelial atrophy Infections
B1 (Thiamine)	Beriberi
B2 (Riboflavin)	Dermatitis and photosensitivity
B3 (Niacin) (Nicotinic acid)	Pellagra*
B12 (Cobalamin)	Pernicious anaemia
C (Ascorbic acid)	Poor wound healing Impaired collagen synthesis
D (Calcitriol) (1,25 DHCC)	Rickets (Children) Osteomalacia (Adults)
K	Clotting disorders

**Diarrhea, Dermatitis, Dementia*

Vitamin B12 Deficiency

Vitamin B12 is mainly used in the body for red blood cell development and also maintenance of the nervous system. It is absorbed after binding to intrinsic factor (secreted from parietal cells in the stomach) and is actively absorbed in the terminal ileum. A small amount of vitamin B12 is passively absorbed without being bound to intrinsic factor.

Causes of vitamin B12 deficiency

- Pernicious anaemia
- Post gastrectomy
- Poor diet
- Disorders of terminal ileum (site of absorption): Crohn's, blind-loop, etc.

Features of vitamin B12 deficiency

- Macrocytic anaemia
- Sore tongue and mouth
- Neurological symptoms: e.g. Ataxia
- Neuropsychiatric symptoms: e.g. Mood disturbances

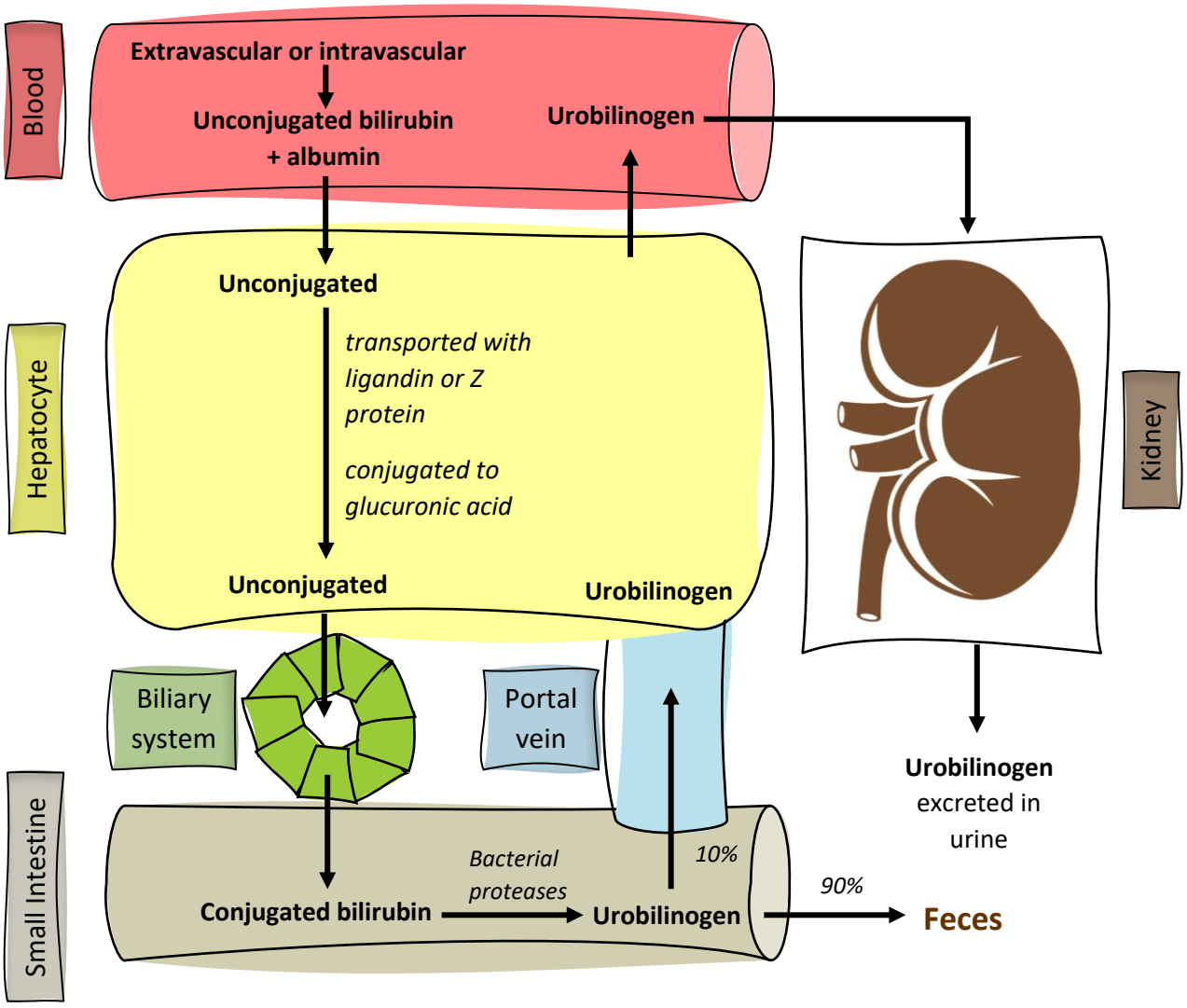
Management

- If no neurological involvement 1 mg of IM hydroxocobalamin 3 times each week for 2 weeks, then once every 3 months.
- If a patient is also deficient in folic acid, then it is important to treat the B12 deficiency first to avoid precipitating subacute combined degeneration of the cord.

Bilirubin metabolism

See hepatobiliary file for Biliary Diseases and Surgical Jaundice

1) Degradation of Hb – bilirubin within spleen
2) Bilirubin binds to albumin in liver *(it is not water soluble)*
3) Within liver, bilirubin conjugated by glucoronyl-transferase *(becomes water soluble)*
4) Secreted into duodenum
5) In distal ileum, bilirubin converted to urobilinogen and excreted in feces as stercobilinogen (giving brown color) or reabsorbed and renally excreted.



Causes of increased anion acidosis: '*MUDPILES*'

- M - Methanol
- U - Uraemia
- D - DKA/AKA
- P - Paraldehyde/phenformin
- I - Iron/INH
- L - Lactic acidosis
- E - Ethylene glycol
- S - Salicylates

Normal Gap Acidosis: *HARDUP*

- H - Hyperalimentation/hyperventilation
- A - Acetazolamide
- R - Renal tubular acidosis
- D - Diarrhoea
- U - Ureteral diversion
- P - Pancreatic fistula/parenteral saline

Causes of Increased FRC:

- Erect position
- Emphysema
- Asthma

Causes of Decreased FRC:

- Pulmonary fibrosis
- Laparoscopic surgery
- Obesity
- Abdominal swelling
- Muscle relaxants

Causes of Increased Serum K+ - *'MACHINE'*

- M - Medications - ACE inhibitors, NSAIDS
- A - Acidosis - Metabolic and respiratory
- C - Cellular destruction - Burns, traumatic injury
- H - Hypoaldosteronism, haemolysis
- I - Intake - Excessive
- N - Nephrons, renal failure
- E - Excretion – Impaired

Causes of severe thrombocytopenia

- ITP
- DIC
- TTP
- Haematological malignancy

Causes of moderate thrombocytopenia

- Heparin induced thrombocytopenia (HIT)
- Drug-induced (e.g. quinine, diuretics, sulphonamides, aspirin, thiazides)
- Alcohol
- Liver disease
- Hypersplenism
- Viral infection (EBV, HIV, hepatitis)
- Pregnancy
- SLE/antiphospholipid syndrome
- Vitamin B12 deficiency

Gastrin
- Increase secretion
  - HCL
  - Pepsinogen
  - IF
- Increases gastric motility
- Trophic effect on gastric mucosa

CCK
- Increases secretion of enzyme-rich fluid from pancreas
- Contraction of gallbladder and relaxation of sphincter of Oddi,
- Decreases gastric emptying,
- Trophic effect on pancreatic acinar cells,
- Induces satiety

Secretin
- Increases secretion of bicarbonate-rich fluid from pancreas and hepatic duct cells
- Decreases gastric acid secretion
- Trophic effect on pancreatic acinar cells

VIP
- Stimulates secretion by pancreas and intestines
- Inhibits acid and pepsinogen secretion

Somatostatin
- Decreases acid and pepsin secretion,
- Decreases gastrin secretion,
- Decreases pancreatic enzyme secretion,
- Decreases insulin and glucagon secretion
- Inhibits trophic effects of gastrin
- Stimulates gastric mucous production

Pancreatic cancer (Adenocarcinoma) risk factors:
- Smoking,
- diabetes,
- Adenoma
- Familial adenomatous polyposis.

Diseases affecting gastric emptying
- Iatrogenic
- Diabetic gastroparesis
- Malignancies
- Congenital Hypertrophic Pyloric Stenosis

Gastric emptying:
Delay emptying
- Gastric inhibitory peptide,
- Cholecystokinin
- Enteroglucagon

Increase emptying
- Gastrin

Osteogenesis imperfect
- Type I the collagen is normal quality but insufficient quantity.
- Type II- poor quantity and quality.
- Type III- Collagen poorly formed, normal quantity.
- Type IV- Sufficient quantity but poor quality

Pancreatic enzymes "L'ATP"
- Trypsinogen,
- Procarboxylase
- Amylase
- Lecithin

Hormones of islets cells of Langerhans
- Beta cells: insulin
- Alpha cells: glucagon
- Delta cells: somatostatin
- F cells: pancreatic polypeptide

The curve is shifted to the Right = Reinforced oxygen delivery to tissues = "All things reinforced i.e. increase"
- Increased temperature
- Increase H^+ (Acidosis)
- Increased DPG: anaemia and high altitude

Shifts to Left = Lower oxygen delivery = "Low, MCH"
- Low 2,3-DPG
- Low temperature
- Low H^+ (alkalosis)
- Low pCO_2
- Methaemoglobin
- Carboxyhaemoglobin
- Hbf
- Polycythemia

Caused of gynecomastia "METOCLOPRAMIDE"
- Metoclopramide
- Ectopic oestrogen
- Trauma skull/tumor breast, testes/ hyperthyroidism / Testicular failure: e.g. Mumps./ Testicular cancer e.g. seminoma secreting HCG
- Orchitis/ Oestrogens
- Cimetidine/ Chlorpromazine / Cannabis / Cushing's
- Liver cirrhosis
- Obesity
- Paraplegia / puberty

R
- Acromegaly / Anabolic steroids / Androgen deficiency: Kalman's, Klinefelter's
- Methyldopa
- Isoniazid
- Digoxin / Dialysis (haemodialysis) / Diuretic (spironolactone: most common drug cause)
- Ethionamide
- Finasteride.

- Very rare drug causes of gynecomastia (My BITCH)
    - Methyldopa
    - Busulfan
    - Isoniazid
    - Tricyclics
    - Calcium channel blockers.
    - Heroin

JVP waveform

- a wave = **a**trial contraction
- c wave = ventricular **c**ontraction, tricuspid valve **c**loses and moves up
- x wave = atrium rela**x**es and tricuspid valve moves down
- v wave = atrial **v**enous filling
- y wave = ventricular filling (The 'y' descent represents the emptying of the atrium and the filling of the right ventricle)

Features of substances used to measure the GFR

- Inert
- Free filtration from the plasma at the glomerulus (not protein bound)
- Not absorbed or secreted at the tubules
- Plasma concentration constant during urine collection

Insulin Function

- Glucose utilization and glycogen synthesis
- Inhibits lipolysis,
- Reduces muscle protein loss

Iron absorption regulation

- Increased by
    - vitamin C
    - gastric acid
- Decreased by (low HCl & 2 Ts)
    - Decreased HCl:
        - Proton pump inhibitors,
        - Gastric achlorhydria,
    - Tetracycline
    - Tannin (found in tea)

Total body iron (4g):

- Hemoglobin: 70%
- Ferritin and hemosiderin: 25%
- Myoglobin: 4%
- Plasma iron: 0.1%

Increased FRC

- Erect position
- Emphysema
- Asthma

Classes of hemorrhagic shock
See before

Decreased FRC

- Lung
    - Pulmonary fibrosis
    - Pulmonary edema
- Muscles
    - Muscle relaxants
    - Reduced muscle tone of the diaphragm
    - Laparoscopic surgery
- Abdominal wall
    - Obesity
    - Abdominal swelling
- Age

Factors affecting stroke volume

- Cardiac size
- Contractility
- Preload
- Afterload

Cortisol Actions

- Glycogenolysis
- Gluconeogenesis
- Protein catabolism
- Lipolysis
- Stress response
- Anti-inflammatory
- Decrease protein in bones
- Increase gastric acid
- Increases neutrophils/platelets/red blood cells
- Inhibits fibroblastic activity

Bony complications of excess glucocorticoids “CALL COLL & NICKIE, CHILDREN of the DIRT”

- Decreased absorption of **cal**cium from the gut
- Vertebral body **coll**apse
- Avascular **nec**rosis
- Growth retardation in **children**
- Increased susceptibility to **infections** “dirt”

Regulation of cortisol

- Increased by “CHLOE STARVED AMerican CATS”
    - **Chole**cystokinin
    - Acetyl**chol**ine
    - Decreased plasma glucose “**starve**”
    - Increased plasma **am**ino acids
    - Sympathetic stimulation and increased **cat**echolamine
- Decreased by “INSULIN, YOU’RE SO FAT”
    - Insulin
    - **Ur**ea
    - **So**matostatin
    - Free **fat**ty acids and ketoacids

Urinary sodium > 20 mmol/l: Sodium depletion, renal loss

- Patient hypovolemic "**DAD**"
  - **D**iuretics (thiazides)
  - **A**ddison's
  - **D**iuretic stage of renal failure
- Patient often euvolemic
  - SIADH

Urinary sodium < 20 mmol/l Sodium depletion, extra-renal loss

- Diarrhea
- Vomiting
- Sweating
- Burns
- Adenoma of rectum

Water excess (patient often hypervolemic and edematous)

- Secondary hyperaldosteronism: CCF, cirrhosis
- Reduced GFR: renal failure
- IV dextrose
- psychogenic polydipsia

Inotrope and its receptor (minor receptor effects in brackets**)**

- Adrenaline: α-1, α-2, β-1, β-2
- Noradrenaline: α-1,(α-2), (β-1), (β-2)
- Dobutamine: β-1, (β 2)
- Dopamine: (α-1), (α-2), (β-1), D-1,D-2

Effects of receptor binding

- α-1, α-2: vasoconstriction
- β-1: increased cardiac contractility and HR
- β-2: vasodilatation
- D-1: renal and spleen vasodilatation
- D-2: inhibits release of noradrenaline

CSF Composition:

- Glucose: 50-80mg/dl
- Protein: 15-40 mg/dl
- Red blood cells: Nil
- White blood cells: 0-3 cells/ mm^3

Factors that may potentiate warfarin

- Liver disease
- P450 enzyme inhibitors
  - amiodarone
  - ciprofloxacin
  - Cranberry juice التوت البري
- Drugs which
  - Displace warfarin from plasma albumin, e.g. NSAIDs.
  - Inhibit platelet function: NSAIDs

Warfarin side effects

- Hemorrhage
- Teratogenic
- Skin necrosis

Raised anion gap metabolic acidosis: CAT MUDPILES

- Carbon monoxide/ Cyanide/ congenital heart failure
- Aminoglycosides
- Theophylline / Toluene (glue sniffing)
- Methanol
- Uremia / Urate
- Diabetic ketoacidosis (also, starvation and alcoholic ketoacidosis)
- Paracetamol/ Phenformin/ Paraldehyde
- Iron / Isoniazid
- Lactic acidosis
- Ethanol / Ethylene glycol
- Salicylate

Normal anion gap (hyperchloremic) metabolic acidosis "SUPER ADDed chloride"

- **S**mall bowel fistula
- **U**reterosigmoidostomy
- **P**ancreatic (and biliary) fistula
- **E**xcess Cl^-
- **R**enal tubular acidosis
- **A**ddison's
- **D**iarrhea
- **D**rugs:
  - carbonic anhydrase inhibitors,
  - K^+-sparing diuretics,
  - acetazolamide,
  - ammonium chloride
  - parenteral nutrition

Metabolic alkalosis: CLEVER PD

- **C**ontraction alkalosis
- **L**iquorice (**glycyrrhizin**) used in hepatitis: (K^+ depletion) / **L**axative abuse
- **E**ndocrine: Conn's/Cushing's/Bartter's: all due to K^+ depletion
- **V**omiting (Cl^- depletion)
- **E**xcess Alkali (e.g. $NaHCO_3$ & antacids)
- **R**efeeding Alkalosis
- **P**ost-hypercapnia (overcompensation): Cl^- depletion
- **D**iuretics: loop and thiazide (Cl^- depletion)

Respiratory Alkalosis: CHAMPS (think speed up breathing)

- **C**NS disease
- **H**ypoxia
- **A**nxiety
- **M**ech Ventilators
- **P**rogesterone
- **S**alicylates/Sepsis

Actions of alfa adrenergic receptors

- Inhibits insulin secretion
- Stimulate glycogenolysis
- Stimulates glycolysis

Actions of beta-adrenergic receptors

- Stimulates glucagon secretion
- Stimulates ACTH
- Stimulates lipolysis

Hyperkalemia: 'Machine'

- M - Medications)
  - By inhibition of aldosterone
    - ACE inhibitors, angiotensin 2 receptor blocker, K-sparing diuretics, heparin
  - Inhibition of renin secretion: NSAIDS, beta blocker (in case of renal failure)
  - Others: ciclosporin, massive blood transfusion,
- A - Acidosis - Metabolic and respiratory, Addison's
- C - Cellular destruction - Burns, rhabdomyolysis, traumatic injury
- H - Hypoaldosteronism, hemolysis
- I - Intake – Excessive
- N - Nephrons, renal failure
- E - Excretion – Impaired

Causes of low magnesium "An END"

- Alcohol
- Electrolytes: Hypokalemia, hypocalcemia
- Total parenteral nutrition
- Diuretics / Diarrhea

Acute phase proteins FACe Him

- Fibrinogen / Ferritin
- Alfa-1 Antitrypsin / serum Amyloid A
- CRP/ Caeruloplasmin / Complement / proCalcitonin
- Haptoglobin

Negative acute phase proteins "CART"

- Cortisol binding protein
- Albumin
- Retinol binding protein
- Transthyretin / Transferrin

Falsely elevated 5-HIAA "MI"

- MAO inhibitors
- Isoniazid

Site of action of diuretics: "FiTS with ADC (عدس)"

- Furosemide: ascending limb of the loop of Henle
- Thiazide: distal tubules
- Spironolactone: cortical collecting tubule

It is anatomically and functionally superior

- The pneumotaxic respiratory center is in the upper pons and it overrides the apneustic center which is found in the lower pons

Central chemoreceptors are stimulated by

- Arterial (not venous) CO_2
- H^+ in the BRAIN INTERSTITIAL fluid

They are not influenced by O_2 and are less sensitive to stimulation by arterial pH.

Stretch & irritant receptors

You need to **stretch** before you run. Running is measured by speed i.e. **rate.** Hence, irritant receptors control bronchospasm

Major functions of spleen in adults

- Iron utilization
- Storage of platelets
- Storage of monocytes
- Hematopoiesis in hematological disorders

Causes of decreased lung compliance (increased: age and emphysema) "it IS FAKE"

- Infection
- Lack of surfactant
- Fibrosis
- Atelectasis
- Kyphosis
- Edema: pulmonary edema
- Ectomy: pneumonectomy

Causes of pseudohaematuria "the Queen Loves Myths & Rome's People"

- Quinine
- Levodopa
- Methyldopa
- Rifampicin
- Phenytoin

Drug causes of SIADH : "SULaFa TRies CARs, CHRISTINa SELECT biCYCLe" & "ABCD"

- Sulfonylureas
- Tricyclics
- Carbamazepine
- vincristine
- Selective SRIs,
- Cyclophosphamide
- Analgesia: opiate and NSAID
- Barbiturate
- Chlorpromazine
- Diuretic (thiazide)

Low TLCO: "FIght 'EM"

- Fibrosis
- Infection
- Embolism
- Emphysema
- Emia: Anemia
- Emptying of the heart: low cardiac out put

Causes of decreased systemic vascular resistance “NSA”

- Neurogenic shock
- Septic shock
- Anaphylactic shock

Hypercalcemia: CHIMPANZEES:

- Calcium supplementation
- Hyperparathyroidism
- Iatrogenic (Drugs: Thiazides)
- Milk Alkali syndrome
- Paget disease of the bone
- Acromegaly and Addison's Disease
- Neoplasia
- Zollinger-Ellison Syndrome (MEN Type I)
- Excessive Vitamin D
- Excessive Vitamin A
- Sarcoidosis

Drugs causing hyperuricemia as a result of reduced excretion of urate: 'Can't leap'. Also, there are: 2 As, 2 anti-TB & 2 Diuretics

- Ciclosporin
- Alcohol
- Nicotinic acid
- Thiazides
- Loop diuretics
- Ethambutol
- Aspirin
- Pyrazinamide

Causes of increased synthesis

- Lesch Nyhan syndrome (Juvenile gout)
- Psoriasis
- Myeloproliferative
- Physiological
    - Diet: rich in purine
    - Exercise

Causes of decreased excretion:

- Preeclampsia
- Renal failure
- Lead

Complications of LMWH (HBO)

- HIT
- Bleeding
- Osteoporosis
- Anaphylaxis

Causes of increased anatomical dead space:

- Increase height of person (standing)
- Increase size of person
- Increase size of airways: bronchodilators
- Increase size of lung (volume)

Causes of increased physiological dead space:

- Increased V/Q: PE, COPD and hypotension