CLINICAL INVESTIGATIONS NOTES

SECOND EDITION

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Table Of Contents:

What's included: Ready-to-study summaries of foundational clinical investigations theory presented in succinct, intuitive and well-diagrammed downloadable PDF documents. Once downloaded, you may choose to either print and bind them, or make annotations digitally on your ipad or tablet PC.

File List:

ABGs - Learning Objectives

Essential

- ✓ Accurately recognise the 7 components of an ABG reading:
  PH, pCO_2, pO_2, HCO_3^-, Base Excess, Anion Gap, p50
- ✓ Be able to calculate the anion gap: $Na^+ - (Cl^- + HCO_3^-)$
- ✓ Understand the role of the three major buffering systems:
  1. Extra cellular ($HCO3^-$ buffer system)
  2. **Intracellular** (H^+ uptake in respiratory acidosis, H^+ dissociation from haemoglobin in respiratory alkalosis)
  3. Bone
- ✓ Understand the role of the r**espiratory** system (alteration of respiratory rate & depth) and **renal** system (excretion of excess H^+ in acidosis or HCO_3^- in alkalosis)
- ✓ Be able to accurately interpret a simple ABG:
- ➢ Accurately recognise an **acidotic** state based on an ABG reading and whether it is **respiratory** or **metabolic**, using DKA and severe COPD as clinical examples
- ➢ Accurately recognise an **alkalotic** state based on an ABG reading and whether it is **respiratory** or **metabolic**, using blood transfusion and pneumonia as clinical examples
- ➢ Accurately recognise a **normal anion gap acidosis** using diarrhoea as a clinical example
- ➢ Accurately recognise a **high anion gap acidosis** using DKA as a clinical example

Important

- ✓ Understand the difference between ABG and VBG

Desirable

- ✓ Understand how the p50 value relates to the Oxygen:Haemoglobin Dissociation curve
- ✓ Understand the physiology of the anion gap

Daily Acid Production

We produce 80 mmol H^+ ions per day, which require to be buffered & excreted to maintain acid:base balance. A small proportion of these H^+ ions are derived from our daily intake of ingested acids (mainly from meat and fish); the majority are produced as by- or end-products of metabolism of proteins, glucose and fats.

Acids derived predominantly from protein metabolism

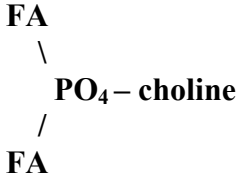
Sulphuric acid H_2SO_4

This is the predominant acid we produce in vivo, making up >50% of the total. It is derived from the catabolism of sulphur-containing amino acids, such as methionine and cysteine.

Phosphoric Acid H_3PO_4

This acid is derived from catabolism of phosphorus-containing substances, such as:

- **Phospholipids** e.g. lecithin



- **Nucleic acids** e.g. DNA, RNA consisting of nucleotides (**Sugar – P – Base)**
- **Adenosine triphosphate** (ATP) **Adenine-ribose-PO_4-PO_4-PO_4**
- **Hydroxyapatite** present in bone & teeth **$Ca_{10}(PO_4)_6OH_2$**

Hippuric Acid Produced as a by-product when Angiotensin I is cleaved to form Angiotensin II

Angiotensin I (10 amino acids)→Angiotensin II (8 amino acids) + Hippuric Acid (2 amino acids)

Uric acid End-product of purine metabolism (adenine & guanine)

Acid derived from glucose metabolism

Lactic Acid

↑Anaerobic glycolysis → accumulation of lactic acid

Glucose
↓
Pyruvate → Lactic Acid

Acids derived from fat metabolism

Fatty Acids (FA) **CH3 - CH2 – CH2 …….COOH** (basic structure of FA)

Ketone Bodies e.g Acetone

Acid derived from carbon dioxide (CO_2)

Carbonic Acid $CO_2 + H_2O \rightarrow H_2CO_3$

ACID-BASE BALANCE

PH is the negative log of H+ concentration (40nmol/L) in the body

$$\begin{aligned} \text{pH} &= -\log 40\text{nmol/L} \\ &= 7.4 \end{aligned}$$

(As a comparison, an average level of potassium in the blood is 4.0 mmol/L = 4,000,000 nmol/L)

The Henderson-Hasselbalch equation

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

It is the *ratio* of HCO_3^- to CO_2 which is important, not the *actual* amounts. The buffering systems, lungs and kidneys all may affect the *ratio*.
The pH of the body is kept within normal limits (7.35 − 7.45) by the response of the *buffer systems of body fluids*, the *respiratory centre* and *kidneys* to changes in acid-base status

- **Buffer systems** (immediate buffering effect, returning pH to normal)
- **Respiratory centre** (within minutes/hours) → Δ in concentration of **CO_2**, by ↑ or ↓ ventilation *
- **Renal system** (within days) → changes in amounts of **HCO_3^-** and **H+** excreted in the urine

*The respiratory centre is 1 – 2x as effective as the ECF buffer system

Buffer Systems

- **Extracellular**
- **Intracellular**
- **Bone**

Extracellular Buffer System

The most important buffer system in the *extracellular* fluid is the ***bicarbonate buffer system***:

$$CO_2 + H_2O \xrightarrow{\text{Carbonic Anhydrase*}} H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

* zinc-containing enzyme → very rapid conversion of carbon dioxide and water to carbonic acid.

If a strong base is added to the system, the OH^- combines with carbonic acid to form $H_2O + HCO_3^-$; thus a strong base is buffered to form a weak base, which can then be safely excreted by the kidneys.

$$OH^- + H_2CO_3 \rightarrow H_2O + HCO_3^-$$

Carbonic acid is a *weak* acid, that is, it does not readily dissociate to provide H+ ions; the HCO_3^- in the system is actually provided by sodium bicarbonate, $NaHCO_3$, which is present in the ECF
Thus:

$$NaHCO_3 \rightarrow Na^+ + HCO_3^-$$

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

If a strong acid is added to the system, the H+ from the acid combines with bicarbonate (from sodium bicarbonate) to form carbonic acid, which dissociates to water & carbon dioxide, which is then expired.
In this way, a strong acid is buffered to form a weak acid (carbonic acid).

Intracellular Buffer Systems

Important *intracellular* buffer systems include:

The Phosphate ($PO_4^{\equiv}$) Buffer System:

$$H^+ + HPO_4^{2-} \rightarrow H_2PO_4^-$$
$$H^+ + H_2PO_4^- \rightarrow H_3PO_4$$

Intracellular proteins, *including haemoglobin:*

$$H^+ + Pr^- \rightarrow HPr$$
$$H^+ + Hb^- \rightarrow HHb$$

Haemoglobin is a better buffer when it is in the deoxygenated form; when oxygen attaches to the haem, a H^+ ion is also acquired →the haemoglobin structure becoming an acid (= hydrogen donor)

2,3 DPG + Hb^- = good buffer
oxygen + HbH = acid

Bone Buffer System

Bone consists of matrix which contains specialised cells (osteoblasts & osteoclasts)

The matrix itself has two components:

- ***organic*** - collagen and other proteins in ground substance
- ***inorganic*** - hydroxyapatite crystals: **$Ca_{10}(PO_4)_6(OH)_2$**

The hydroxyapatite crystals make up two-thirds of the total bone volume; they are extremely small and consequently have a huge total surface area. The crystals contain a large amount of carbonate **(CO_3^{-2}).**

CO_2 in bone is in two forms:

1. Bicarbonate (HCO_3^-)
2. Carbonate (CO_3^{2-}).

The bicarbonate makes up a readily exchangeable pool because it is present in the fluid which makes up the 'hydration shell' around each of the hydroxyapatite crystals. The carbonate is present in the crystals and its release requires dissolution of the crystals. This is a much slower process but the amounts of buffer involved are much larger.

Thus two processes are involved in the bone buffer system:

- Ionic exchange
- Dissolution of bone crystals

Ionic exchange – involves peri-crystallar fluid
Bone can *take up* H^+ in exchange for Na^+ and K^+ or *release* HCO_3^-
Dissolution of bone crystals:
CO_3^{2-} or HPO_4^{2-} is released and can buffer H+ ions

In acute metabolic acidosis uptake of H^+ by bone in exchange for Na^+ and K^+can occur rapidly without any bone breakdown.
In chronic metabolic acidosis, the major buffering mechanism is release of calcium carbonate from bone. Renal tubular acidosis, uraemia & endstage COPD are associated with longterm acidosis and may result in osteomalacia/osteoporosis as a result of breakdown of the hydroxyapatite crystals.

Renal response to a change in acid:base status

Each day, 4320 mEq HCO_3^- are filtered by the glomeruli; normally, almost all is reabsorbed thereby conserving the primary buffer system in the body.

For each mEq of HCO_3^- to be reabsorbed, *one mEq H+* must be secreted into the tubular lumen to combine with the HCO_3^- anion (bicarbonate must be converted to carbonic acid before it can be absorbed).

Thus *4320mEq H+ need to be secreted each day* just to allow the HCO_3^- to be reabsorbed; in addition *a further 80 mEq H+* must be secreted to rid the body of H+ ions derived from the non-volatile acids produced daily by the body's metabolic processes, e.g. lactate, phosphate, sulphate, acetoacetate & β-hydroxybutyrate. Therefore, *4400mEq H+ need to be secreted by tubular cells/day.* (4320 + 80 mEq/L)

When there is **alkalosis** (↓ H+ /↑ HCO_3^- in ECF), the kidneys fail to reabsorb all the filtered HCO_3^- (because there is an excess of HCO_3^- in the lumen compared to H+, all the H+ is used up combining with the HCO_3^- and the remaining HCO_3^- cannot be absorbed into the tubular cell unless it is converted to H_2CO_3, so is lost in the urine.)

Conversely, in **acidosis**, all the filtered HCO_3^- is reabsorbed and new HCO_3^- is formed and returns to the ECF, and buffers the excess H+ ions there.

New HCO_3^- is generated in the following way:

Excess H+ secreted into the tubular lumen combines with phosphate or ammonia rather than $HCO3^-$ (because all filtered $HCO3^-$ has been reabsorbed) and is excreted as NaH2PO4 and NH4+; this shifts the bicarbonate buffer system within the tubular cell to the right, and a new $HCO3^-$ is formed for each H+ buffered in this way.

In the PCT, H+ is transported across the luminal membrane attached to a carrier protein, which it shares with Na+. (As Na+ enters the cell, H+ passes out into the lumen) The energy for this process is derived from the movement of Na+ ions down the concentration gradient for Na+ which has been formed by the Na:K pump situated in the membrane of the contralateral side of the tubular cell. Its function is to actively pump Na+ out of the cell and K+ into it, in a ratio of 3 : 2. This creates a negative charge within the cell, and a fall in Na+ concentration, hence → influx of Na+ ions from the tubular lumen into the cell.

In DCT and collecting ducts, H+ is actively secreted into the lumen by a specific protein, the energy being supplied by conversion of ATP → ADP. It is this mechanism which is most effective in acidification of the urine.

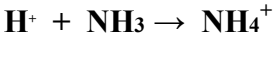
There are 3 important buffer systems in the kidney:

1. The bicarbonate system *within the tubular cells*
2. The phosphate system *in the tubular lumen*

NaH_2PO_4 = titratable acidity (TA)
Total acid excretion = $(TA + NH_4^+) - HCO_3^-$

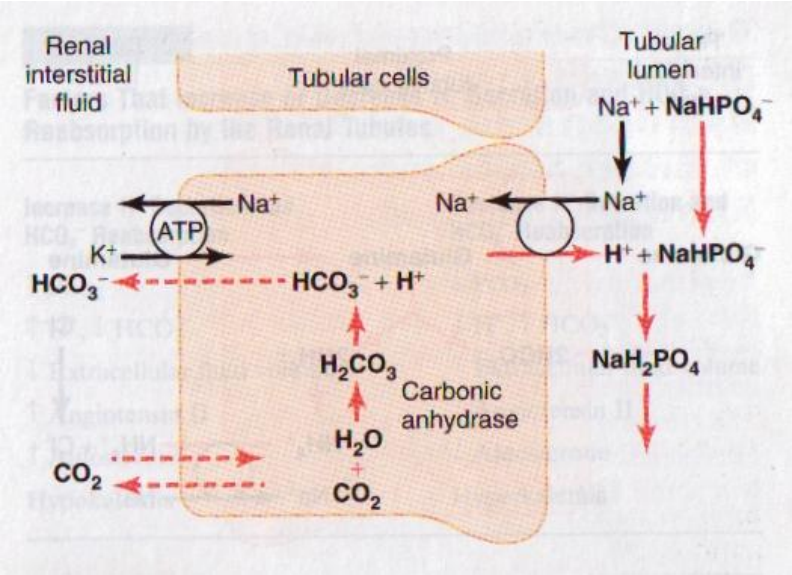
(Phosphate is filtered as the sodium salt ($NaHPO_4^-$) at a rate of 30 – 40 mEq/day)

3. The ammonia buffer system *within the tubular cells (in PCT, Loop of Henle and DCT)* and *in the tubular lumen (in the collecting ducts)*, is quantitatively more important than the phosphate buffer system:



In the proximal parts of the nephron, the amino acid, glutamine, is absorbed *into the tubular cells* where it is metabolised to produce ammonia (NH_3) which combines with H+ → NH_4^+. This is then secreted → tubular lumen and passes out in the urine.

In the collecting ducts, H+ combines with NH_3 *in the lumen* (NH_3 being freely diffusible across the tubular cell membrane). The NH4+ thus formed, cannot diffuse back into the tubular cell, and passes out in the urine.



Buffering of secreted H+ ions by filtered phosphate ($NaHPO_4^-$)
Note that a new bicarbonate is returned to the blood for each $NaHPO_4^-$ that reacts with a secreted hydrogen ion.

Characteristics of Acid-Base Disturbances

	PH	PCO_2	HCO_3^-
Normal	**7.4**	**40mmHg**	**24mEq/L**
Respiratory acidosis	↓	↑↑	↑
Respiratory alkalosis	↑	↓↓	↓
Metabolic acidosis	↓	↓	↓↓
Metabolic alkalosis	↑	↑	↑↑

Acute changes in H+ ion concentration affect the **Oxygen : Haemoglobin Dissociation Curve** (Bohr effect), acidosis shifting the curve to the right, alkalosis to the left.

K+ and H+ concentrations in ECF parallel each other:

Hypokalaemia is associated with alkalosis **($\downarrow K^+$, $\downarrow H^+$)**
When hypokalaemia is present, potassium is preferentially reabsorbed in the renal tubules in exchange for H+, which is then lost in the urine, resulting in metabolic alkalosis; when an individual is alkalotic (that is, the H+ concentration in the blood is too low) H+ moves from the intra-cellular to the extra-cellular fluid in exchange for K+, hence resulting in hypokalaemia.

Hyperkalaemia is associated with acidosis **($\uparrow K^+$, $\uparrow H^+$)**
In a situation of acidosis (increased H+ concentration in ECF), intracellular buffering of H+ ions takes place in exchange for K+, which then accumulates in the ECF.

Predominant ECF ions: **Sodium, chloride, bicarbonate**
Predominant ICF ions: **Potassium, phosphate, proteins, magnesium, sulphate (PPPMS)**

H^+ and **HCO_3^-** can diffuse in and out of cells, but do so *slowly*.

Definition of Base Excess

The amount of base that requires to be added to or removed from 1L of blood to restore the pH to 7.4 at a PCO_2 of 40 mm Hg

It follows that these measurements are only helpful in ascertaining the *metabolic* causes of acid-base disturbances, since any respiratory contribution to the acid:base disturbance has been removed by restoring the PCO_2 to 40 mmHg.

The Anion Gap

The anion gap is the difference in number between the positively and negatively charged ions used in the formula below, the cation level (sodium) being greater than the sum of the level of the two anions (bicarbonate and chloride)

$$\text{Anion Gap} = (Na^+) - (HCO_3^- + Cl^-)$$

If we take average normal values for these ions and calculate the anion gap using this formula, it becomes clear how the anion gap value is obtained.

Ion	Normal range
Sodium	**135 – 145 mmol/L**
Bicarbonate	**22 – 33 mmol/L**
Chloride	**100 – 110 mmol/L**
Anion Gap	**4 − 13 mmol/L**

Anion Gap = 140 − (25 + 105) mmol/L
= 140 − 130 mmol/L
= 10 mmol/L

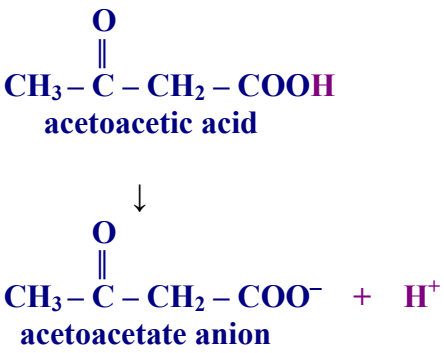
There is no *real* anion gap in the plasma, as the total number of positively and negatively charged ions balance each other out exactly. It is simply a manmade formula which is helpful to determine the cause of a metabolic acidosis, as it tells us whether the acidosis has been caused by:

- an excess of acid — e.g. ketoacids in diabetic ketoacidosis:
  or
- a loss of bicarbonate from the body — e.g. diarrhoea

Metabolic acidosis caused by excess of acid (High anion gap metabolic acidosis)

Diabetic ketoacidosis (DKA) is an example of a high anion gap metabolic acidosis.
When, for example, acetoacetic acid accumulates in DKA, it donates its hydrogen ion to the plasma, and the anion (acetoacetate) is formed; the hydrogen ion is buffered by plasma bicarbonate.

Figure: Structure of acetoacetic acid



Thus the plasma bicarbonate level falls. For each hydrogen ion buffered, there is a corresponding fall in bicarbonate level, and the loss of this negatively charged anion from the plasma is replaced by the anion of the acid donating the hydrogen ion, in this case, acetoacetate, thus maintaining electrical neutrality in the plasma.

The HCO_3^- level falls in both a high anion gap metabolic acidosis and a normal anion gap metabolic acidosis; in a high anion gap metabolic acidosis, this is due to the plasma bicarbonate being consumed as a buffer for the added acid – there is no change in the levels of the other two measured ions, that is, the sodium or the chloride ions.

e.g. 140 − (15 + 105)
= 140 − 120
= 20 mmol/L

Metabolic acidosis caused by loss of bicarbonate (Normal anion gap metabolic acidosis)

In a normal anion gap metabolic acidosis, the bicarbonate level falls, not because it is being used as a buffer for the added acid, but because it is being lost from the body, either from the GIT as in diarrhoea, or via the kidney in renal tubular acidosis or Addison's disease. There is no added acid to the plasma to provide a mmol of anion for each mmol fall in bicarbonate, so the loss of anion (bicarbonate) must be balanced by an increase in the plasma chloride level, resulting in the so-called "hyperchloraemic metabolic acidosis"
Because chloride is one of the ions used in the formula, and as its level increases as the bicarbonate level decreases, the total number of anions in the formula remains the same.

e.g. **140 − (15 + 115)**
140 − 130
10 mmol/L

Causes of a high anion gap acidosis

"**KUSMAL"**

(Kussmaul breathing = deep, sighing respiration of acidosis)

Adolf Kussmaul, German physician, 19th century.

K Ketoacidosis
U Uraemia
S Salicylic acid
M Methanol
A Antifreeze (ethylene glycol)
L Lactic acid

Ketoacidosis:	Acetone, acetoacetic, beta-hydroxybutyric acids eg DKA Starvation Catabolism of alcohol → beta-hydroxybutyric acid
Uraemia:	In CKD, the kidneys are unable to adequately excrete the daily acid load produced by metabolic processes
Salicylates	Salicylic acid, lactic acid and ketones in 25% of cases
Methanol	Formic acid (used in drink spiking)
Antifreeze (Ethylene glycol)	Oxalic and glycolic acids
Lactic Acidosis:	Poor perfusion e.g. shock Alcoholism (↑NADH → formation of lactic acid from pyruvate) Iatrogenic (Phenformin) Bowel ischaemia / infarction

Causes of a normal anion gap acidosis

Diarrhoea	(commonest cause of metabolic acidosis overall) Due to loss of bicarbonate from the GIT.
Renal tubular acidosis (RTA)	↓Tubular secretion of H^+ &/or ↑renal loss of HCO_3^-
Addison's Disease	↓Mineralocorticoid effect →↑renal loss of Na^+ (and water), ↓tubular secretion of H^+, ↑renal loss of HCO_3^-

Causes of Metabolic Alkalosis

(An *uncommon* acid:base disturbance)

1. Loss of acid

From the stomach ▫ vomiting gastric contents/nasogastric suction

From the kidneys ▫ ↑Aldosterone

e.g. Diuretics
Cushings syndrome
Conn's syndrome
Excessive licorice ingestion
Corticosteroid treatment

▫ Hypokalaemia→ preferential absorption of K+ in tubules in exchange for H+

2. Addition of alkali

▫ IV Bicarbonate, used in the treatment of severe metabolic acidosis
▫ Citrate in a large blood transfusion

(Aldosterone → Na^+ reabsorption in exchange for H^+ and K^+ → hypokalaemic metabolic alkalosis)

Causes of Respiratory Acidosis

· Lung disease resulting in:

▫ inadequate transfer of CO_2 across respiratory membrane e.g. COPD, late stage asthma
▫ obstruction to expiration e.g. laryngo-tracheo-bronchitis, foreign body, strangulation

· ↓Chest wall movement e.g. intercostal muscle paralysis as in Guillain-Barre syndrome, quadriplegia, Myasthenia gravis; phrenic nerve palsy, ankylosing spondylitis, chest pain e.g. from fractured ribs

· Respiratory centre depression e.g. use of opiates

Causes of Respiratory Alkalosis

Any cause of tachypnoea, such as:
· anxiety
· pneumonia
· hepatic failure (ammonia & other substances normally metabolised by the liver stimulate the respiratory centre)
· pregnancy (progesterone stimulates the respiratory centre)
· mechanical ventilation

Buffering in Acid:Base Disturbances

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

Buffering means that a strong acid (one which readily donates its H+) is exchanged for a weak one (carbonic acid) which is much less ready to donate its H+ and instead dissociates into $H_2O + CO_2$, which is then expired. The anion of such an acid then causes an elevation in the anion gap.

If a strong alkali is added to the body, it is converted to a weak one (bicarbonate) which can then be readily excreted by the kidneys.

Buffering of metabolic acid:base disturbances takes place partially in the ECF, (bicarbonate buffer system), partially in the intracellular compartment (phosphate, protein buffers), and partially by the bone buffer system.

•Metabolic Acidosis

Excess metabolic acid (high anion gap acidosis) :

◦ ECF buffering:

H+ donated by the acid is buffered by bicarbonate in the ECF:

$$\uparrow CO_2 + \uparrow H_2O \leftarrow \uparrow H_2CO_3 \leftarrow \overset{H^+}{\underset{+}{HCO_3^-}} + H^+$$

◦ Respiratory compensation:

The $\uparrow PCO_2$ and the ↑H+ concentration stimulate the respiratory centre → ↑ventilation rate → $\uparrow CO_2$ expired (Kussmaul respiration)

Therefore: $\downarrow\downarrow HCO_3^-$ (used up in buffering process)
$\downarrow PCO_2$ (compensation)

◦ Renal compensation:
As the excess H+ is excreted, for each ion passing out in the urine, a new bicarbonate ion is formed and enters the ECF

Loss of bicarbonate (normal anion gap acidosis):

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow \downarrow HCO_3^- + H^+$$

Insufficient HCO_3^- is present in ECF to buffer the daily H+ production → $\uparrow H^+$ concentration (acidosis)

◦ Chloride level ↑ to maintain electrical neutrality

◦ Respiratory compensation:
The ↑H+ concentration stimulates the chemoreceptors in aorta and carotid artery and the respiratory centre → ↑ventilation rate → $\uparrow CO_2$ expired (Kussmaul respiration)

◦ Renal compensation: As in high anion gap metabolic acidosis

•Metabolic Alkalosis

Caused by loss of acid/gain of alkali (bicarbonate or other e.g. citrate)

Loss of acid:

$$CO_2 + H_2O \overset{*CA}{\leftrightarrow} H_2CO_3 \leftrightarrow HCO_3^- + \downarrow H^+$$

◦ Respiratory compensation:

The ↓H+ concentration inhibits the respiratory centre → ↓ventilation rate → CO_2 retained so equation → right so H^+↑ (and bicarbonate ↑ secondarily)

*CA = carbonic anhydrase

◦ Renal compensation

Too little H^+ for reabsorption of all filtered bicarbonate so balance lost in urine → a fall in HCO_3^- in ECF

Addition of alkali other than HCO_3^-:

$$H_2CO_3 \overset{OH^-}{\rightarrow} \uparrow HCO_3^- + H_2O$$

◦ ECF buffering

The excess HCO_3^- combines with H^+ → $\downarrow H^+$

Thus, even though the equation will shift to the left, the respiratory centre responds to the fall in H+ concentration by decreasing the respiratory rate. (The respiratory centre is more sensitive to H+ concentration than it is to P_{CO_2} level)

◦ Respiratory and Renal compensation:

Same as in alkalosis caused by loss of acid

→ retention of CO2
→ loss of HCO_3^- in urine

Addition of bicarbonate:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow \uparrow HCO_3^- + H^+$$

◦ Compensation: Same as above

•Respiratory Acidosis

$$\uparrow CO_2 + H_2O \rightarrow \uparrow H_2CO_3 \rightarrow \uparrow HCO_3^- + \uparrow H^+$$

◦ Intracellular buffering:

H+ is buffered intracellularly by haemoglobin, other proteins and $PO4^{\equiv}$

Buffering of respiratory acid:base disturbances takes place ± purely intracellularly, predominantly by haemoglobin. The bicarbonate buffer system is not involved.

◦ Renal compensation:

In the kidneys, once all the bicarbonate has been absorbed, excess H+ is secreted into tubular lumen (buffered by phosphate and ammonia), and for each H+ secreted, a bicarbonate ion re-enters the circulation.

•Respiratory Alkalosis

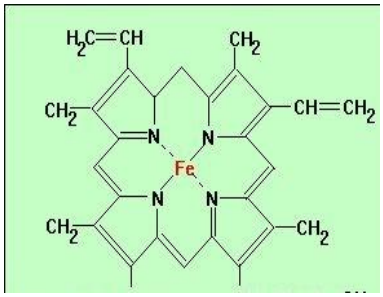
$$\downarrow CO_2 + H_2O \rightarrow \downarrow H_2CO_3 \rightarrow \downarrow HCO_3^- + \downarrow H^+$$

Buffering as such does not take place. A fall in the PCO_2 causes the haemoglobin molecule to donate a H^+ ion, which diffuses from inside the red cell into the ECF→ helping to elevate the H^+ concentration.

◦ Renal compensation:

At the renal level, there is less H^+ available for bicarbonate reabsorption in the tubules → loss of bicarbonate in urine → $\downarrow HCO_3^-$ in ECF

P50



Haem portion of haemoglobin

Oxygen attaches to the ferrous (++) iron in the centre of the porphyrin ring structure of haem. (This is a non-ionic bond)

The P50 is the partial pressure of oxygen in the blood when haemoglobin is 50% saturated with oxygen. When the position of the oxygen:haemoglobin dissociation curve is normal, that is, when the bond between oxygen and haemoglobin is of normal strength, the P50 value is 24mmHg – 28 mmHg. If the curve is shifted to the right, this means that the bond is weaker than normal, and that oxygen more readily dissociates from haemoglobin as it passes through the tissues, and oxygen delivery is therefore improved. In this situation, the P50 value is > 28mmHg.

When the curve is left-shifted, the affinity of haemoglobin and oxygen is increased (stronger binding) and oxygen delivery at tissue level is therefore decreased. The P50 value is < 24mmHg. As the blood flows past the respiratory membrane the haemoglobin avidly takes up oxygen when the curve is in the leftward position.

In summary, the P50 shows us the position of the curve, and infers the quality of oxygen delivery to the tissues.

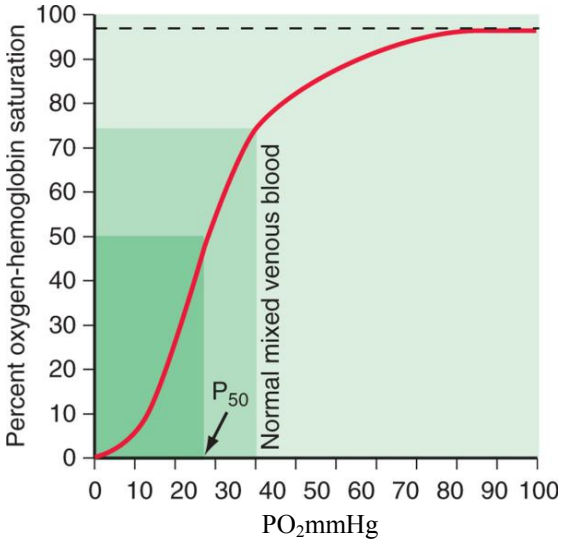
Factors which shift the curve to the right do so by exerting a conformational change in the haemoglobin molecule by binding to the globin chain.This change lessens the strength of the bond between the iron and oxygen.

Factors → right shift

↑H+
↑CO2
↑Temperature
↑2,3 Diphosphoglycerate (2,3 DPG)

Factors → left shift

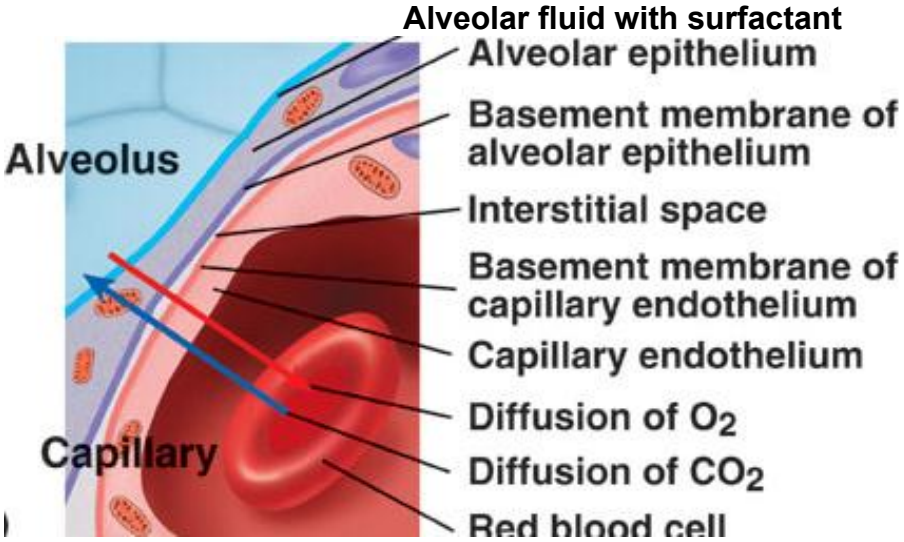
↓H+
↓CO2
↓Temperature
↓2,3 DPG
Carbon monoxide
Foetal haemoglobin (Hb F)
Methaemoglobinaemia



Oxygen-haemoglobin dissociation curve.

The P_{50} of adult blood is 24 - 28 mmHg. Under basal conditions, mixed venous blood has PO_2 of 40 mmHg and oxygen-haemoglobin saturation of 75%. In arterial blood, these values are 100 mmHg and 97.5%, respectively.

The Respiratory Membrane



RESPIRATORY Pathology:
ABGs & OXIMETRY

PULSE OXIMETRY - *KNOW*:

- **Relationship Between O2 Sats & pO2:**
  - Higher the O2 Sats, the Higher the pO2
- **Shape of the Oxygen-Hb-Dissociation Curve:**
  - Plateau favours O2 loading @ High pO2
  - Steep part favours O2 Unloading @ Low pO2
- **Shifting the Oxygen-Hb-Dissociation Curve:**
  - **pH –** (Acid → Right-Shift → Favours O_2 Unloading)
  - **P_{CO2}** – (High P_{CO2} → Right-Shift → Favours O_2 Unloading) ("Bohr effect")
  - **BPG** (Bisphosphoglycerate) – (Hypoxia → ↑BPG → Right-Shift → Favours O_2 Unloading)
  - **Temperature –** (Exercise → ↑2-3°C → Right-Shift → Favours O_2 Unloading)
- **Why is Oxygen Important?**
  - Essential for aerobic cell function
  - Some cells (with no aerobic capacity – Neurons/Myocytes) are damaged very quickly if hypoxic.
- **Symptoms @ Different Arterial PO_2's:**
  - PaO2 of 90 mmHg - normal person with no symptoms
  - PaO2 of 55 mmHg - short term memory loss, euphoria, impaired judgement
  - PaO2 of 30 -55 mmHg - progressive loss of cognitive and motor function
  - PaO2 < 30 mmHg - loss of consciousness

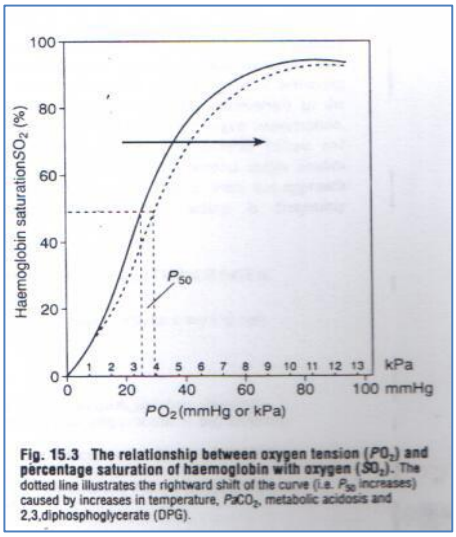


Fig. 15.3 The relationship between oxygen tension (PO_2) and percentage saturation of haemoglobin with oxygen (SO_2). The dotted line illustrates the rightward shift of the curve (i.e. P_{50} increases) caused by increases in temperature, $PaCO_2$, metabolic acidosis and 2,3,diphosphoglycerate (DPG).

O2-Haemoglobin dissociation curve

Saturation %	PaO2 mmHg	Significance
97%	100	normal
90%	60	"cusp"
75%	40	venous
50%	26	

Be able to reproduce both of the above.

Arterial Blood Gas:

- **Provides Information on:**
  - Oxygenation & Ventilation (pO2 and pCO2)
    - *i or Insp* = Inspired gas
    - *a or Art* = Arterial blood
    - *A or Alv* = Alveolar gas
    - *No Prefix* = Arterial Blood
  - Acid/Base Disturbance
  - Hb
- **Significant Measurements:**
  - pH
  - pCO_2
  - pO_2
  - HCO_3
  - Base Excess
  - A-a Gradient
- **Normal Values:**
  - pH : 7.35 – 7.45
  - pO_2 : 70-100 mmHg
  - pCO2 : 35 – 45 mmHg
  - HCO3 : 22 – 26 mmol/L (arterial) and 24 – 28 mmol/L (venous)
  - BE : -3 to +3
    - The Base Excess = The amount of base needed to be Added/Removed to restore the pH to 7.4 with the pCO2 held constant at 40mmHg. It is a representation of the metabolic component of any acid base disturbance.
- **What Specific Abnormal Values Tell Us:**
  - **Acidosis:**
    - pH less than 7.35
    - **Can be Respiratory or Metabolic:**
      - **Respiratory** – Due to Alveolar Hypoventilation (→↑$paCO_2$)
        - Compensated for by Metabolic Mechanisms (Ie. Retaining Base)
      - **Metabolic** – Due to Gain of Acid *OR* Loss of Base
        - Compensated Rapidly by Respiratory Mechanisms (Ie. Blowing off CO_2)
  - **Alkalosis:**
    - pH more than 7.45
    - **Can be Respiratory or Metabolic:**
      - **Respiratory** – Due to Alveolar Hyperventilation (→↓$paCO_2$)
        - Compensated by Metabolic Mechanisms (Ie. Excreting Base)
      - **Metabolic** – Due to Loss of Acid (Eg. Acute Vomiting)
        - Compensated Rapidly by Respiratory Mechanisms (Ie. Retaining CO_2 Hypoventilation)
  - **Compensation?:**
    - Remember the Bicarbonate Buffer system:
      - H+ + HCO3- ⇔ H2CO3 ⇔ CO2 + H2O
    - **Acidosis** (more H+) can be buffered by forcing the equation to the right:
      - Adding HCO3-
      - or Lowering CO2
    - **Alkalosis** (less H+) can be buffered by forcing the equation to the left:
      - Adding H+
      - or Hypoventilating (to raise CO2)

- **Anion Gap:**
  - (The difference between Measured Cations and Unmeasured Anions (including acids))
  - Anion gap is used to narrow down the causes of metabolic acidosis:
    - High Anion Gap Metabolic Acidosis is due to ↑Concentration of Unmeasured Anions:
      - Lactic Acidosis
      - Ketoacidosis
      - Renal Failure (Uraemia)
    - Normal Anion Gap Metabolic Acidosis is due to Loss of HCO_3 from the body.
      - Renal Losses (Eg. Renal Tubular Acidosis)
      - GIT Losses (Eg. Diarrhoea)
- **A-a Gradient:**
  - Gap between the Calculated Alveolar pO2 and the Measured Arterial pO2.(taken from the arterial blood gas)
  - (A-a) Gradient = pAlvO2 – pArtO2
  - **Normally less than 12**
  - Abnormal (A-a) gradient = V/Q Mismatch (Ie. Lungs aren't exchanging air)

- **6 Steps to Interpretation of Arterial Blood Gas (ABG) Results:**

1) **What is the pH**
   - Is this an acidosis or an alkalosis ?
2) **Is Co2 Responsible**
   - Is the change in pCO2 consistent with the dominant acid base disturbance ?
     - If it is then this is a respiratory acidosis or alkalosis.
     - If it is not then it is a metabolic acidosis or alkalosis.
3) **Is HCO3 responsible?**
   - Is the change in H2CO3 consistent with the dominant acid base disturbance ?
4) **State the primary Disturbance**
   - Is this an acidosis or an alkalosis ?
5) **Look for compensation**
   - **Look at the Base Excess.**
     - (Base Excess = the amount of base that you'd need to add to make the pH normal if he CO2 was normal in that patient)
     - (*Abnormal Base Excess = Metabolic Component*)
     - If it is > +3 then it is a metabolic alkalosis.
       - (Excess Base or Deficit of Acid)
     - If it is < -3 then it is a metabolic acidosis.
       - (Deficit of Base or Excess Acid)
   - **Look at the pCO2 & H2CO3**
     - Is there any respiratory compensation? (signs of Hyper/Hypo-Ventilation?)
     - Is there any metabolic compensation? (signs of H2CO3 Excretion/Retention?)
6) **Final analysis**
   - State your findings

- **Arterial Blood Gas Example Cases:**
  - **CASE 1** – A student practising arterial blood gas sampling on another student.
    - PH 7.40
    - PCO2 40 mmHg
    - PO2 95 mmHg
    - HCO3- 27 mmol/l
    - Base Excess -1
  - Normal

  - **CASE 2** – A 38 year old male who has been found unconscious after taking an overdose.
    - PH 6.95
    - PCO2 85 mmHg
    - PO2 40 mmHg
    - HCO3- 33 mmol/l
    - Base Excess +2
  - 1. It is an Acidosis
  - 2. PCO_2 is elevated (Consistent with Acidosis) → Respiratory Acidosis
  - 3. Base Excess is Normal → No Metabolic Component

  - **CASE 3** – A 17 year old who has become very upset after a fight with friends.
    - PH 7.7
    - PCO2 10 mmHg
    - PO2 110 mmHg
    - HCO3- 24 mmHg
    - Base Excess -2
  - 1. It is an Alkalosis
  - 2. PCO_2 is Low (Consistent with Alkalosis) → Respiratory Alkalosis
  - 3. Base Excess is Normal → No Metabolic Component

  - **CASE 4** – A 27 year old female diabetic with vomiting and feeling unwell.
    - PH 7.2
    - PCO2 25 mmHg
    - PO2 98 mmHg
    - HCO3- 14 mmol/l
    - Base Excess -12
  - 1. It is an Acidosis
  - 2. PCO_2 is Low (*Not* Consistent with Acidosis) → Metabolic Acidosis
  - 3. Base Excess is Abnormal → Metabolic Component
    - -12 → Metabolic Acidosis

  - **CASE 5** – A 54 year old male with diarrhoea.
    - PH 7.6
    - PCO2 46 mmHg
    - PO2 74 mmHg
    - HCO3- 39 mmol/l
    - Base Excess + 10
  - 1. It is an Alkalosis
  - 2. PCO_2 is Normal (Not Consistent with Alkalosis) → Metabolic Alkalosis
  - 3. Base Excess is Abnormal → Metabolic Component
    - + 10 → Metabolic Alkalosis

- **CASE 6** 70 year old man, short of breath
  - pH 7.25
  - CO2 90
  - O2 60
  - HCO3 38
  - Base Excess +10
- 1. It is an Acidosis
- 2. PCO_2 is High (Consistent with Acidosis) → Respiratory Acidosis
- 3. Base Excess is Abnormal → Metabolic Component
  - +10 → A Metabolic Alkalosis (Compensating for the Respiratory Acidosis; Confirmed by the high HCO_3)
  - :. Respiratory Acidosis with Metabolic Compensation

- **More Arterial Blood Gasses Cases:**
  - Ph 7.3
  - CO2 – 70 (Resp Acidosis)
  - HCO3 – 30
  - Base excess = +8 (Metabolic Alkalosis)
  - Therefore – Respiratory acidosis with Metabolic compensation

  - Ph 7.2
  - O2 – 105
  - CO2 – 16 (Respiratory Compensation)
  - HCO3 – 10
  - Base excess = -16 (Metabolic Acidosis)
  - Metabolic Acidosis with Respiratory compensation

  - Ph 7.2
  - O2 - 60
  - CO2 - 80 (Respiratory Acidosis)
  - HCO3 - 28
  - Base Excess = -1 (No metabolic compensation)
  - Acute Respiratory Acidosis with no Metabolic Compensation

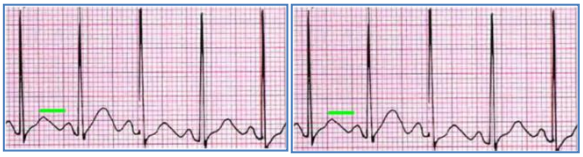
  - pH 7.6
  - O2 - 97
  - CO2 - 15
  - HCO3 - 20
  - Base excess = +2
  - Respiratory Alkalosis due to Hyperventilation

  - 7.13 Acidosis
  - CO2 - 43
  - HCO3 - 18
  - Base Excess = -31 (Metabolic Acidosis)
  - Metabolic Acidosis (However he isn't compensating by breathing(Which he should be)) → About to have a respiratory arrest (Very sick)

Dysrhythmias (Arrhythmias):

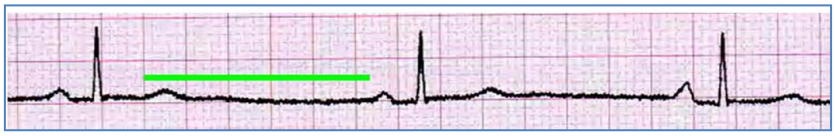
Atrial Arrhythmias:

- **Sinus Tachycardia:**
  - **Causes:**
    - ↑Cardiostimulation (Sympathetic)
    - ↓Cardioinhibition (Parasympathetic)
    - Hyperthyroidism
    - Fever/Infection/Inflammation
    - Heart Failure/Shock/Hypovolaemia
    - PE
    - MI
  - **Features:**
    - = Sinus Rhythm of >100^{+}Beats/min
      - All waves visible
      - P-Waves Precede All QRS Complexes
    - Shortened Q-T Interval (But still <1/2 RR Interval)
    - Shortened T-P Interval

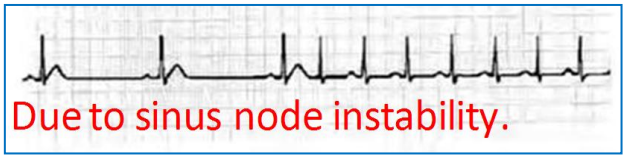


(NB: In this example, there are high voltage QRS = Abnormal – Probably Vent. Hypertrophy)

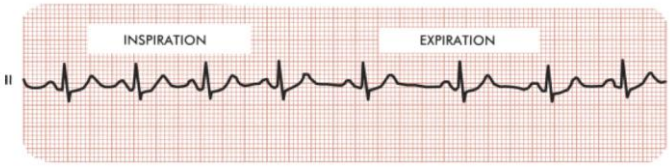
- **Sinus Bradycardia:**
  - **Causes:**
    - ↓Cardiostimulation (Sympathetic)
    - ↑Cardioinhibition (Parasympathetic)
    - Hypothyroidism
    - Athletes
    - Drugs (eg. B-Blockers, Ca-Blockers)
    - Hyperkalaemia
    - Elderly (Sick Sinus Syndrome)
  - **Features:**
    - = Sinus Rhythm of <60 Beats/min (SA-Node is still the pacemaker)
      - All waves visible
      - P-Waves Precede All QRS Complexes
    - Prolonged Q-T Interval (But still <1/2 RR Interval)
    - Prolonged T-P Interval



- **Brady-Tachy Syndrome:**
  - **Causes:**
    - Due to SA-Node Instability
    - Common in Elderly
  - **Features:**
    - Intermittent Episodes of Sinus Bradycardia & Sinus Tachycardia

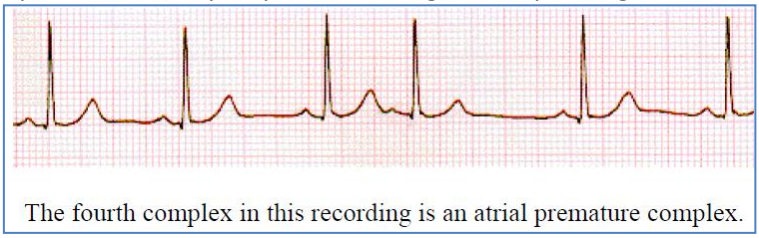


- **Sinus Arrhythmia (Physiological):**
  - **Causes:**
    - Healthy People – Typically Young People
    - Respiratory Sinus Arrhythmia
  - **Features:**
    - ↑HR with Inspiration
    - ↓HR with Expiration



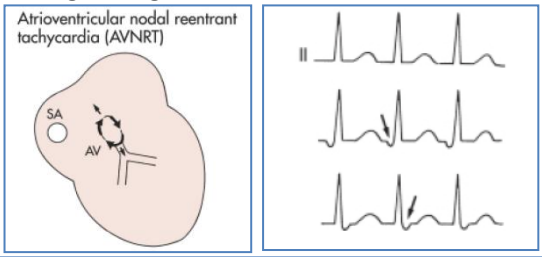
Respiratory sinus arrhythmia.

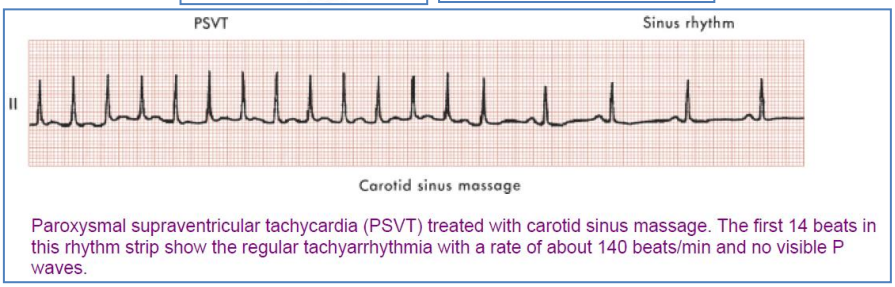
- **Atrial Premature Beats (Atrial Ectopics):**
  - **Causes:**
    - Atrial Ectopic Focus depolarises the Atria before Sinus Node is due to Fire Again.
      - Stress
      - Caffeine, Sympathomimetics
      - Hyperthyroidism
  - **Features:**
    - Shortened RR-Interval Preceding APB, then Long RR-Interval Directly After
    - Ectopic P-Wave (may be positive or negative depending on location of ectopic focus)



The fourth complex in this recording is an atrial premature complex.

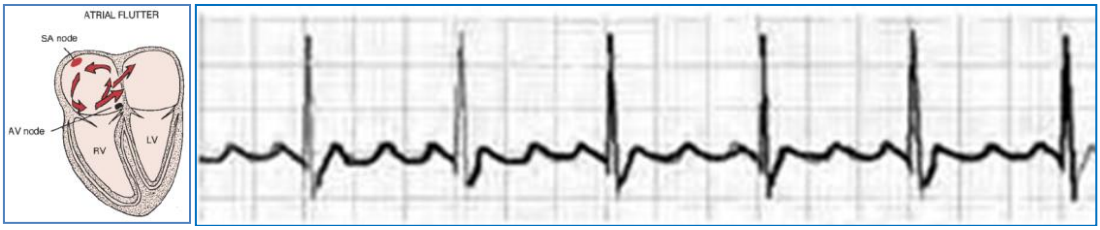
- **Supraventricular Tachycardias:**
  - **Causes:**
    - AV Nodal Re-Entry Circuit
  - **Features:**
    - >100bpm BUT <250bpm. (Usually ≈130bpm)
    - No Discernable P-Wave (Due to Simultaneous Atrial & Ventricular Depolarisation)
      - But may see part of the *Negative* P-Wave just before/after the QRS.
  - **Diagnosis: (Adenosine)**
    - Adenosine – has a –ve Dromotropic Effect (Slows SA-Node). Therefore if Ventricular Rate slows, the origin of the Tachycardia is in the Atria. If Ventricular Rate remains constant, the Tachycardia is originating elsewhere and therefore not a SVT.



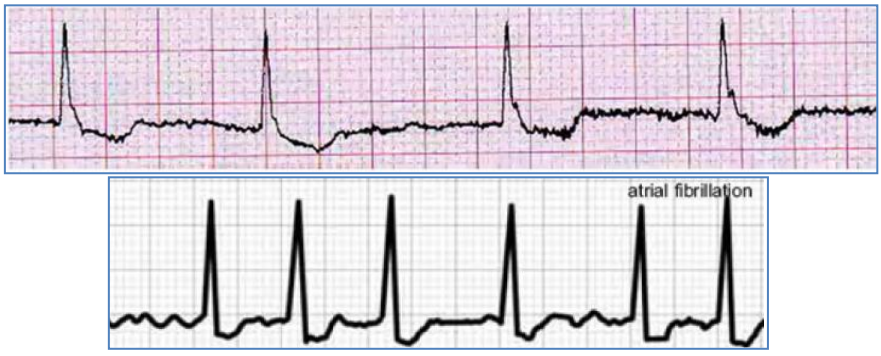


Paroxysmal supraventricular tachycardia (PSVT) treated with carotid sinus massage. The first 14 beats in this rhythm strip show the regular tachyarrhythmia with a rate of about 140 beats/min and no visible P waves.

- **Atrial Flutter:**
  - **Causes:**
    - Anticlockwise Wide Re-Entry Circuit around the Whole Atrium
    - Mitral Regurg/Stenosis, IHD, HTN, CHF, COPD, PE.
  - **Features:**
    - Atrial Rate ≈ 250-350bpm (Typically ≈300bpm)
    - Ventricular Rate ≈ 75-150bpm (Due to 2:1, 3:1, or 4:1 AV Block)
    - Sawtooth Flutter-Waves
  - **Treatment:**
    - Cardioversion to Restore Rhythm (the use of an electric shock to convert a dangerously rapid, fluttering, and ineffective heartbeat to its normal rhythm) – Different to Defib.

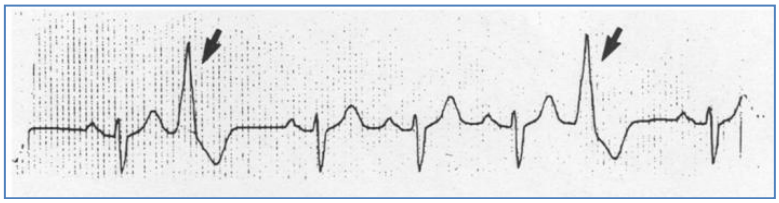


- **Atrial Fibrillation:**
  - **Causes:**
    - Atrial Dilation/Enlargement (CHF, HTN, Pul.HTN, COPD, PE)
    - IHD
    - Thyrotoxicosis
    - Alcoholism
    - Pericarditis
    - Hypoxia
  - **Features:**
    - Atrial Rate ≈ 350-600Beats/min
    - Ventricular Rate = Irregular but Tachy.
    - P-Waves are Unclear
    - Irregularly Irregular QRS
  - **Treatment:**
    - Ventricular Rate Control
    - Restoration of Sinus Rhythm (Via Cardioversion/Defibrillation)
    - Anticoagulant Drugs. (To prevent Clots)

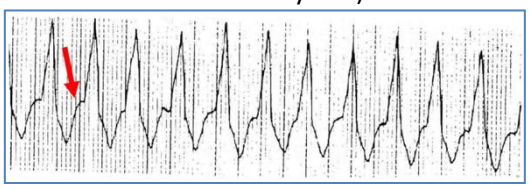


Ventricular Arrhythmias:

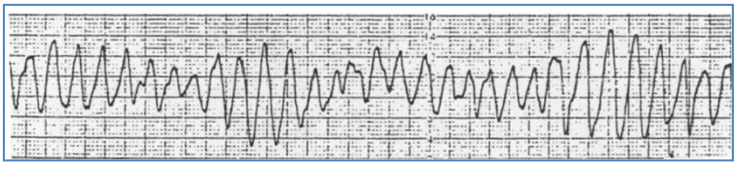
- **VPBs - Ventricular Premature Beats / PVCs - Premature Ventricular Complexes:**
  - **Causes:**
    - Ventricular Ectopic Focus (Re-Entry)
    - Elderly
    - Anxiety, Caffeine, Sympathomimetics, Digoxin
    - Hypokalaemia
    - Acute MI
  - **Features:**
    - Wide QRS-Complex (Vent.Depolarisation Complex)
    - No Preceding P-Wave.
    - Deep S-Wave & T-Wave Inversion
    - NB: – Consecutive Premature Ventricular Complexes = Ventricular Tachycardia.



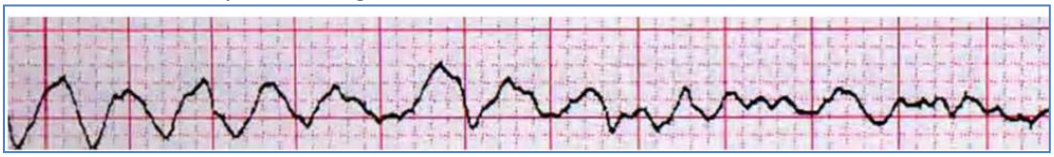
- **Ventricular Tachycardias:**
  - **Causes:**
    - Continual Ventricular Ectopic Focus (Re-Entry)
    - Prior MI → Fibrotic Focus → Provides Circuit for Re-Entry
  - **Features:**
    - 100-300bpm
    - >3 Consecutive VPBs (PVCs) - Consecutive ***Tall, Wide QRS-Complexes***
      - *Non-Sustained* VT = <30s duration
      - *Sustained* VT = >30s duration
    - No Discernable P-Waves
    - + T-Wave Inversion
  - **Treatment:**
    - Anti-Arrhythmic Drugs
    - Cardioversion (the use of an electric shock to convert a dangerously rapid, fluttering, and ineffective heartbeat to its normal rhythm) timed with R-Wave



- **Polymorphyic VT ("Torsades De Points"):**
  - **Causes:**
    - Mechanism not fully understood
    - Acute Ischaemia
    - Long-QT-Syndrome (An inherited ion channel mutation)
    - (Drugs) eg. K^+ Channel Blockers
    - Electrolyte Disturbances.
  - **Features:**
    - 100-300bpm
    - VT with QRS-Complexes of Changing Amplitude
    - No P Waves
    - No T Waves

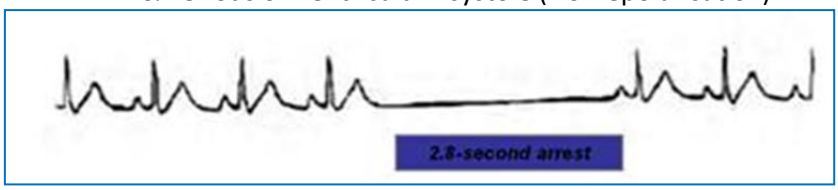


- **Ventricular Fibrillation:**
    - **Causes:**
        - Degeneration from PVC → VT → VF
        - Acute MI
        - Digoxin Toxicity
        - Epinephrine/Cocaine
        - Hypokalaemia/K^+ Blockers
        - Electrocution
        - AF with WPW.
    - **Features:**
        - Disordered, rapid Ventricular Depolarisation with No Coordinated Contraction → No Cardiac Output →Life Threatening!
            - → Dyspnoea
            - → Unconscious.
        - Chaotic, irregular appearance.
        - No discernible QRS Complexes, P-Waves or T-Waves
    - **Treatment:**
        - Defibrillation – Much more powerful than cardioversion & isn't timed with R-Wave
        - Anti-Arrhythmic Drugs.

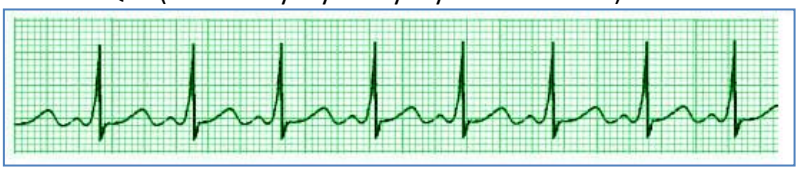


Disorders of Conduction:

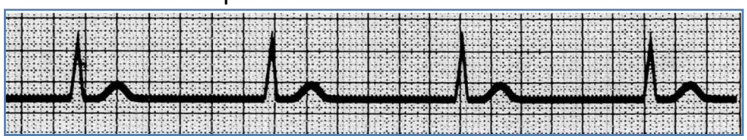
- **SA-Node Arrest:**
  - **Causes:**
    - Hypoxia
    - MI/IHD
    - Hyperkalaemia (Lethal Injection)
    - Vasovagal Episode
  - **Features:**
    - Complete Failure of the SA-Node to discharge
      - → Absence of Atrial Depolarisation
      - → & Periods of Ventricular Asystole (No Depolarisation)



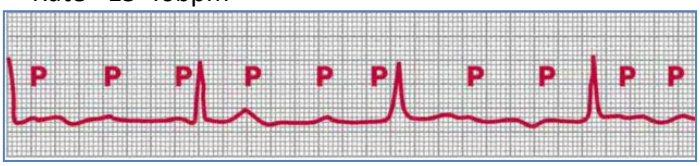
- **Accessory Pathways – Eg. Wolf-Parkinson-White:**
  - **Causes:**
    - Congenital Accessory Pathway Bypassing the AV-Node
  - **Features:**
    - Short PR-Interval
    - Delta Wave (Pre-excitation of Purkinje Fibres)
    - Widened QRS (Due to Myocyte-Myocyte Conduction)



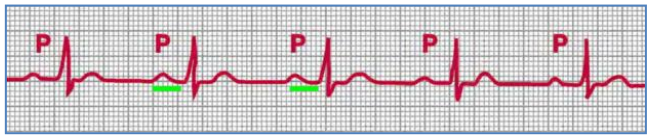
- **Escape Rhythms:**
  - **Causes:**
    - **1.** SA-Node Failure (No P-Wave) → AV-Node takes over → *Rate* ≈ 40-60bpm
    - **2.** Complete Heart Block (AV-Node Failure) → Bundle Branches Take over →Rate ≈15-40bpm
  - **Features:**
    - **1. Atrial (AV-Nodal) Escape Rhythm:**
      - No Preceding P-Waves
      - Rate ≈ 40-60bpm



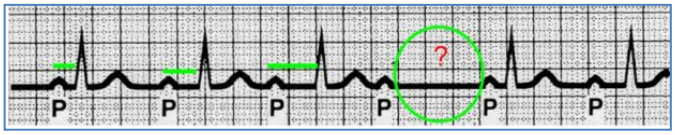
    - **2. Ventricular Escape Rhythm:**
      - Complete Heart Block: No Relationship between P-Waves & QRS.
      - Rate ≈15-40bpm

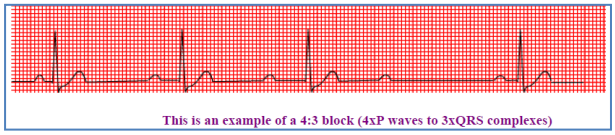


- **AV-Conduction Blocks → 1 of 3 Degrees:**
  - **1. First-Degree Heart Block:**
    - **Causes:**
      - Old Age
      - IHD
      - Myocarditis
      - Digoxin, B-Blockers
    - **Features:**
      - Increased AV Delay → Prolonged PR-Interval (>5mm = >0.20sec)
      - NB: a 1:1 Relationship between P-Waves & QRS-Complex is Maintained.

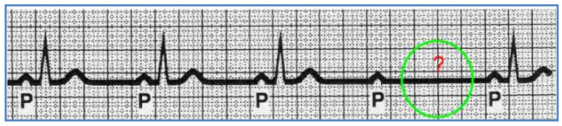


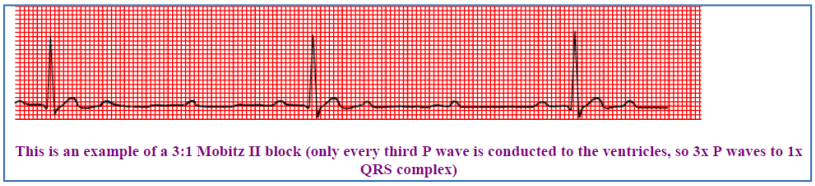
  - **2. Second-Degree (Mobiz) Heart Blocks:**
    - **Mobiz Type-I ("Wenckebach"):**
      - **Causes:**
        - Inferior MI
        - B-Blockers, Ca-Blockers
        - ↑Vagal Tone
      - **Features:**
        - AV-Conduction Failure with Gradual Lengthening of PR-Interval.
        - (Ie. Some P-Waves aren't followed by QRS-Complexes)



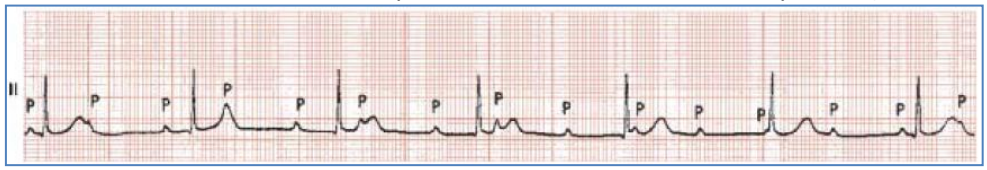

This is an example of a 4:3 block (4xP waves to 3xQRS complexes)

    - **Mobiz Type-II:**
      - **Causes:**
        - Anteroseptal or Inferior MI
        - NB: Always Pathological & can → Complete Heart Block.
      - **Features:**
        - = Intermittent AV-Conduction Failure without Lengthening of PR-Interval. (PR-Interval is Fixed)
        - Block may last for 2/more beats.

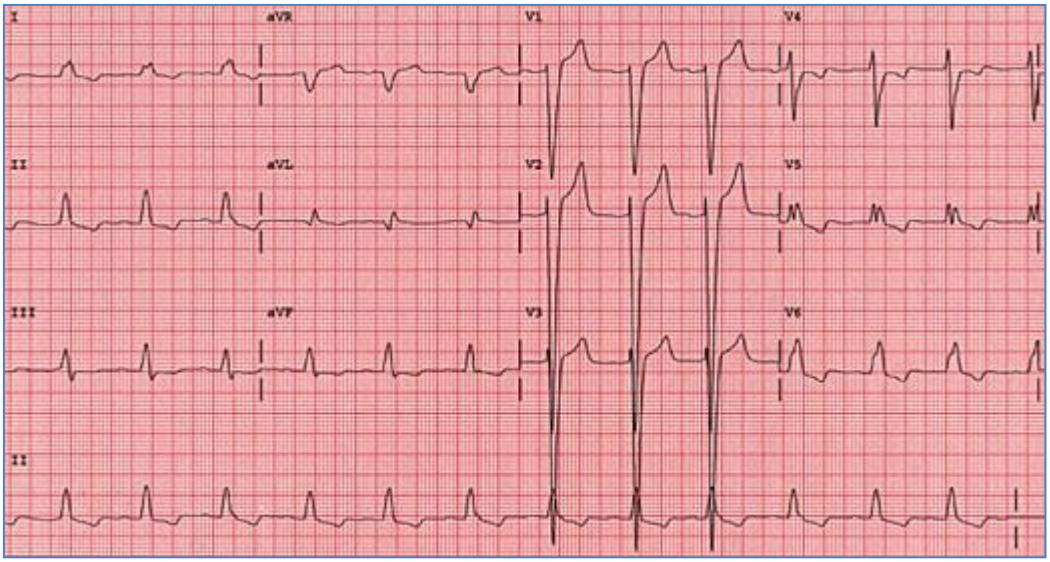



This is an example of a 3:1 Mobitz II block (only every third P wave is conducted to the ventricles, so 3x P waves to 1x QRS complex)

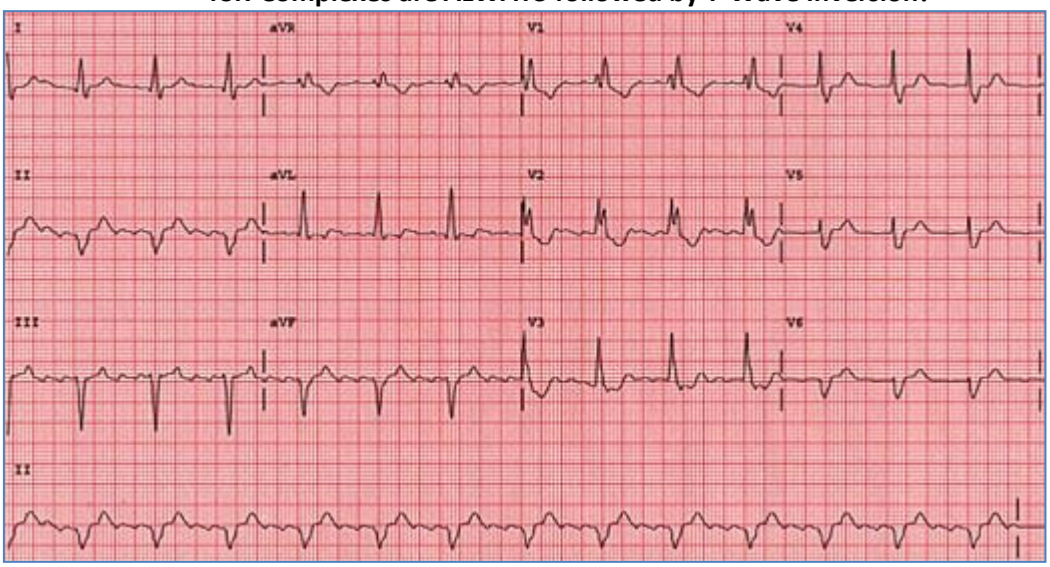
  - **3. Third-Degree Heart Block (AKA: Complete Heart Block):**
    - **Causes:**
      - IHD
      - Digoxin Tox
      - ASD/VSD
      - Congenital
      - NB: Survival Requires an Artificial Pacemaker.
    - **Features:**
      - = Complete conduction failure between Atria & Ventricles.
      - Regular P-Waves
      - But No relationship between P-Waves & QRS-Complexes. (Both occur sporadically)



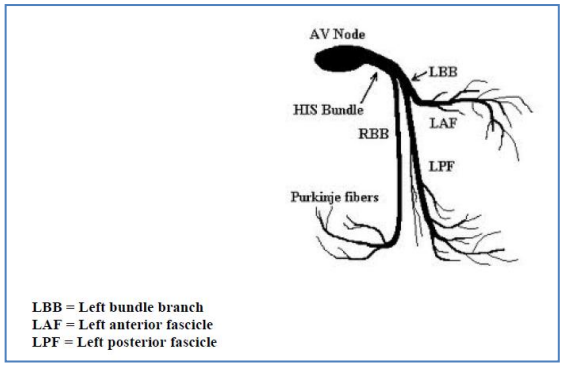
- **Bundle Branch (Lateral) Blocks (Ie. @ L/R Bundle-Branches):**
  - **Left Bundle-Branch Block:**
    - **Causes:**
      - HTN
      - IHD
      - Elderly Degeneration
      - Mitral/Aortic Valve Disease
    - **Features:**
      - Wide QRS (Often Notched = **"rSR Complexes"**)
      - **W**illia**M** (QRS is **Negative/W-Shaped in V1 *AND* Positive/M-Shaped in V6**)
      - **rSR-Complexes are *ALWAYS* followed by T-Wave Inversion!**

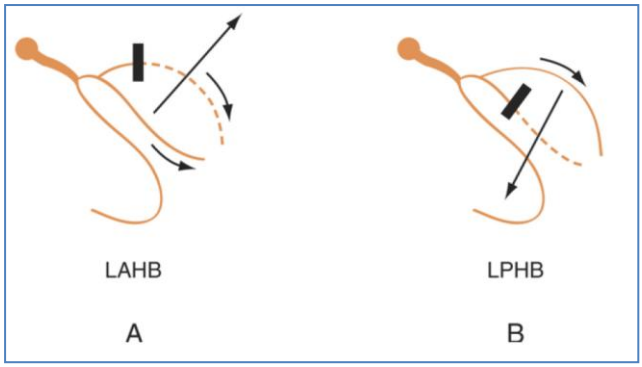


  - **Right Bundle-Branch Block:**
    - **Causes:**
      - Pulmonary HTN (Eg. COPD/PE)
      - Tricuspid/Pulmonary Valve Disease
      - Elderly Degeneration
    - **Features:**
      - Wide QRS (Often Notched = **"rSR Complexes"**)
      - **M**orro**W** (QRS is **Positive/M-Shaped in V1 *AND* Negative/W-Shaped in V6**)
      - **rSR-Complexes are *ALWAYS* followed by T-Wave Inversion!**



- **LBB Fascicular Blocks:**
    - **Causes:**
        - IHD
        - Ageing Heart
        - Drugs
        - LVH
        - HTN
    - **Left-*Anterior* Fascicular Block:**
        - **Features:**
            - LAxD
            - NB: No Wide QRS (Since Signal is still Conductile)
    - **Left-*Posterior* Fasicular Block:**
        - **Features:**
            - RAxD
            - NB: No Wide QRS (Since Signal is still Conductile)





CLINICAL INVESTIGATIONS

The following topics will be discussed during the Clinical Investigations tutorials:

- Electrocardiogram (ECG)
- Arterial Blood Gases (ABG)
- Pulmonary Function Tests (PFT)
- Liver Function Tests (LFT)
- Full Blood Count (FBC)
- Renal Function Tests

ECG - Learning objectives

Essential

Pre reading

- ✓ *Correctly identify major anatomical features of the heart :4 chambers, valves, major vessels (aorta, vena cavae, pulmonary vessels) conducting system, main coronary arteries.*
- ✓ *Understand the orientation of the heart in the thorax*

In course

- ✓ Correctly identify which ECG leads correspond to which anatomical part of heart
- ✓ Know how each feature of ECG corresponds to underlying cardiac electrical activity
- ✓ Correctly identify the following features on an ECG:
- o Calibration
- o Rate (n.b. be able to 'eyeball' rate as well as accurately calculate)
- o Rhythm : sinus/not sinus
- o Axis
- o Major arrhythmias: sinus tachycardia, sinus bradycardia, AF, VF, ectopic beats
- o LBBB, RBBB, first degree heart block
- o Chamber hypertrophy
- o Ischaemic changes: ST segment and T wave changes (stable angina pectoris and varying degrees of ACS including unstable angina, STEMI and non-STEMI)
- o Effect of abnormalities in electrolyte levels particularly potassium and calcium

Desirable

Correctly identify the following features in an ECG:

- o Pericarditis
- o 2^{nd} + 3^{rd} degree block
- o VT + SVT
- o Pulmonary embolism
- o Low voltage (hypothyroidism, pericardial effusion, obesity, COPD)
- o QT changes including congenital prolonged QT
- o Wolf-Parkinson-White syndrome
- o Pacemaker spikes and complexes
- o Atrial flutter

ECG Tutorials

1. History of the ECG.
2. Information obtained from an ECG
3. Anatomy of the heart
4. Orientation of leads
5. ECG paper
6. ECG interpretation: (15 points)

1. History

The ECG has been in use for over a century. A British physiologist, Augustus Waller, performed the first ECG recording in 1887, and he gave demonstrations of his technique, using his dog, Jimmy, as the "patient". Einthoven, from Holland, was present at such a demonstration. Willem Einthoven constructed his well-known triangle and the hexaxial system to help us gain further insight into the electrical activity of the heart.

2. Information obtainable from an ECG

ECGs can give us much information about the heart and also give us clues about other aspects of an individual's state of health, such as:

Rhythm – sinus/non-sinus
Conduction – normal/abnormal
Size of heart chambers
Presence of ischaemic heart disease
Pulmonary embolism
Inflammation of the pericardium/effusion
Emphysema
Drugs the patient may be on e.g. Digoxin, Calcium channel blockers
Electrolyte status of the patient – potassium, calcium levels
Temperature – pyrexia or hypothermia
Endocrine status – AF in thyrotoxicosis; bradycardia in hypothyroidism
Raised intracranial pressure

In ischaemic heart disease, the ECG may give us several pieces of information, such as:

• The *location* of the affected area of myocardium (in order of frequency)
Antero-septal area
Inferior surface of the heart
Antero-lateral aspect of the left ventricle etc

•*Whether the full thickness of the ventricular wall or only part of it is involved*

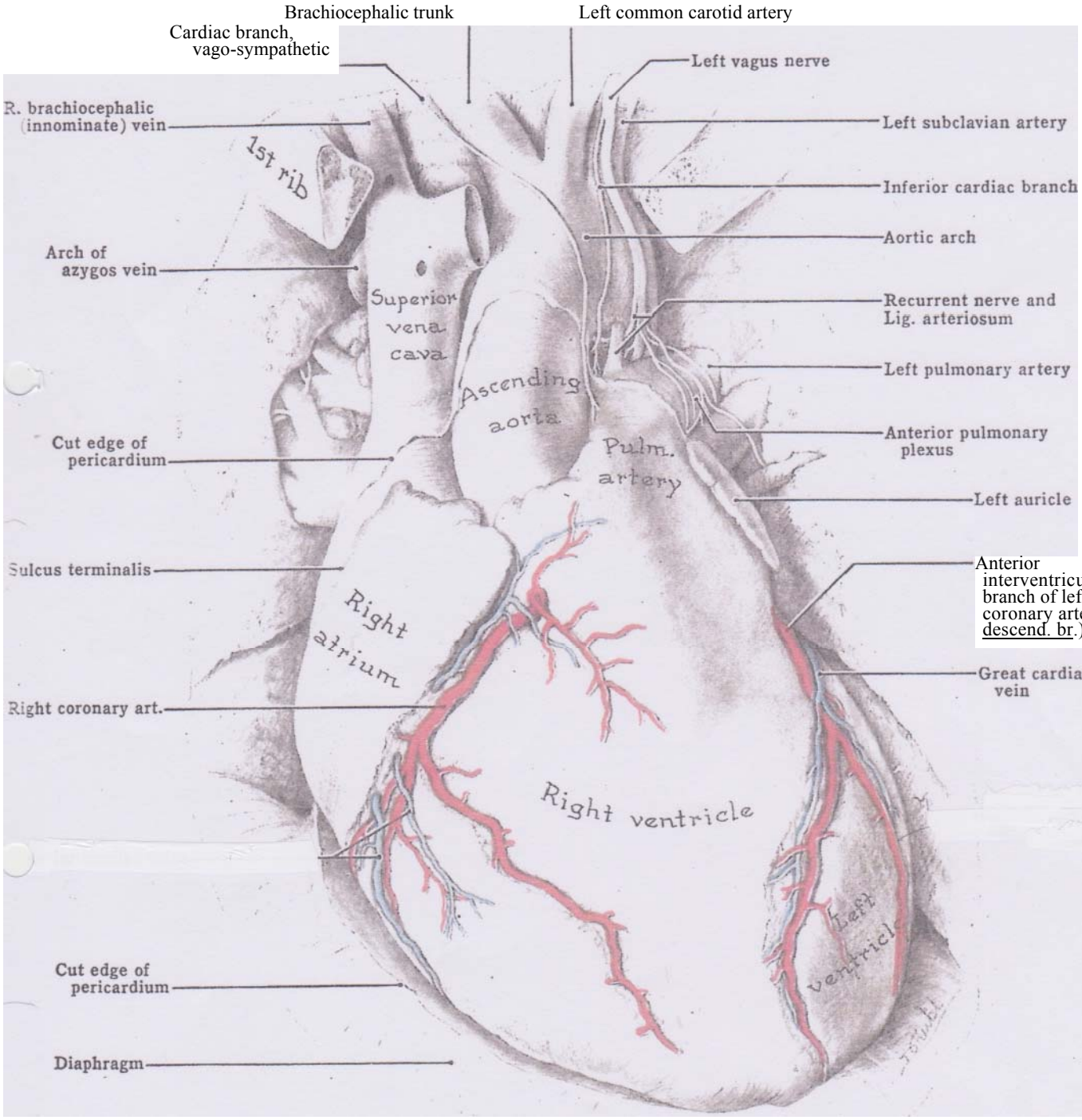
This is made evident by the presence or absence of pathological Q waves, and the situation of the ST segment. (ST elevation in transmural infarction; ST depression in sub-endocardial MI)

• Whether there are any obvious *sequelae* of the infarction, such as:

Cardiac failure (sinus tachycardia)
Rhythm abnormalities
Left ventricular aneurysm (persistently elevated ST segment)

3. Anatomy of the heart

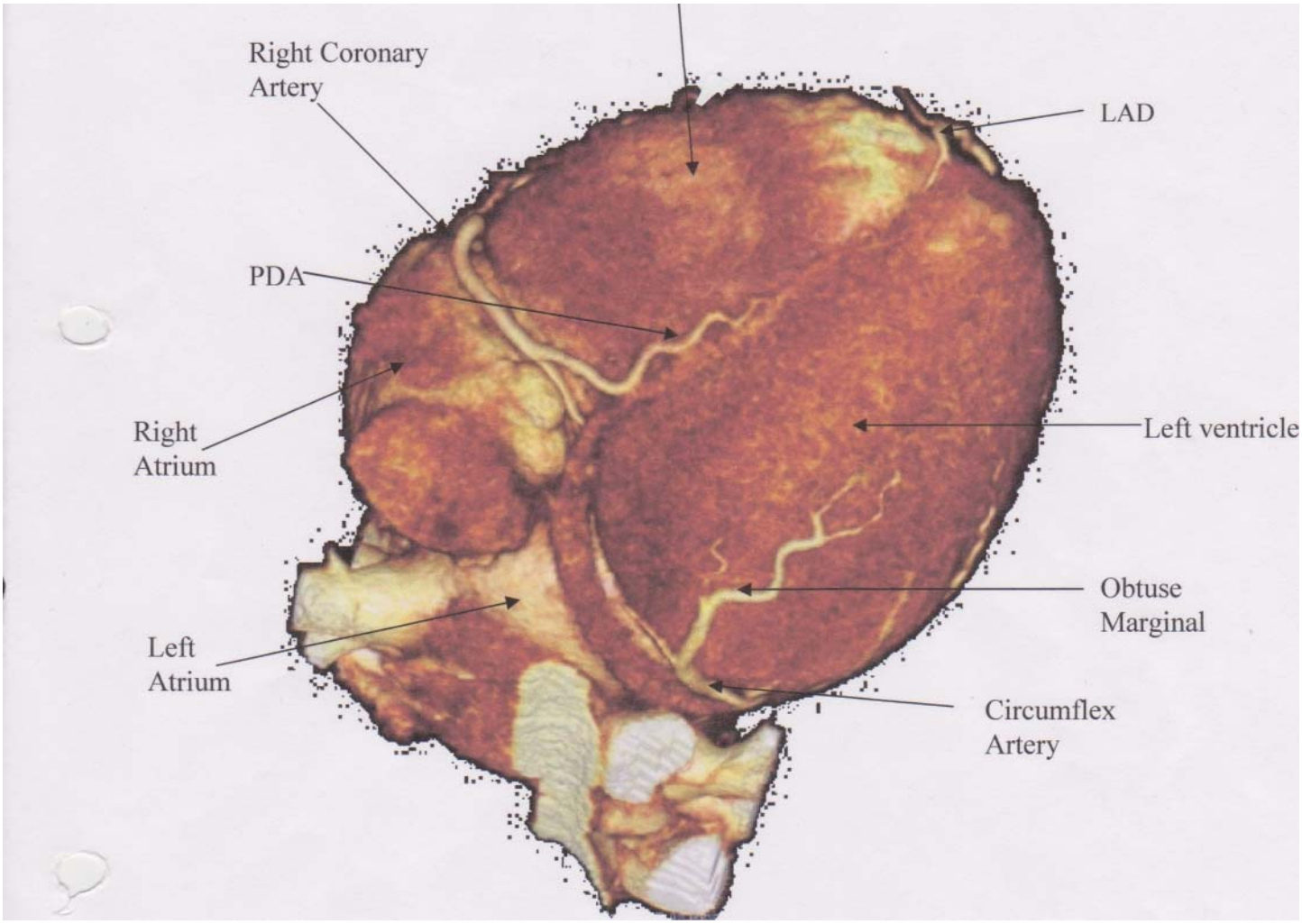
I



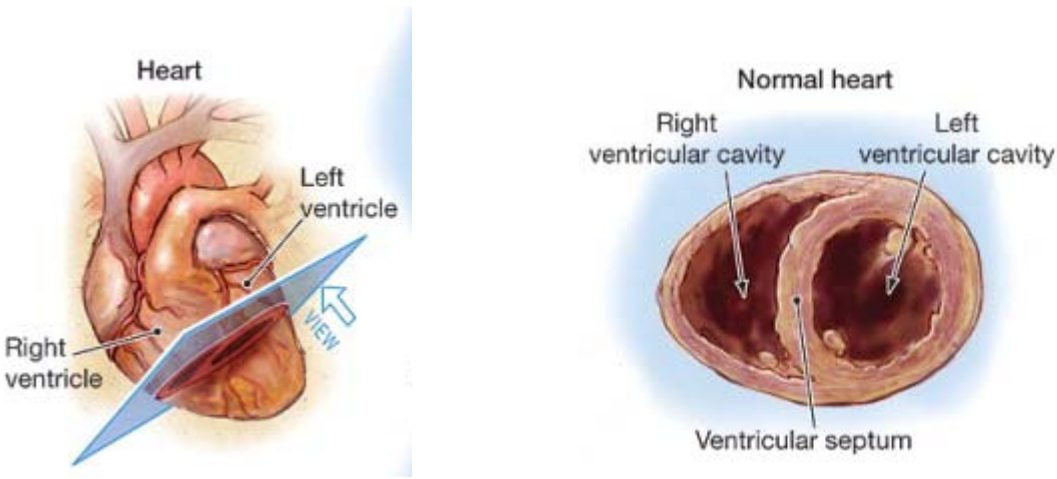
Heart and Great Vessels

Sternocostal Aspect

Right ventricle



Infero-posterior aspect of the heart

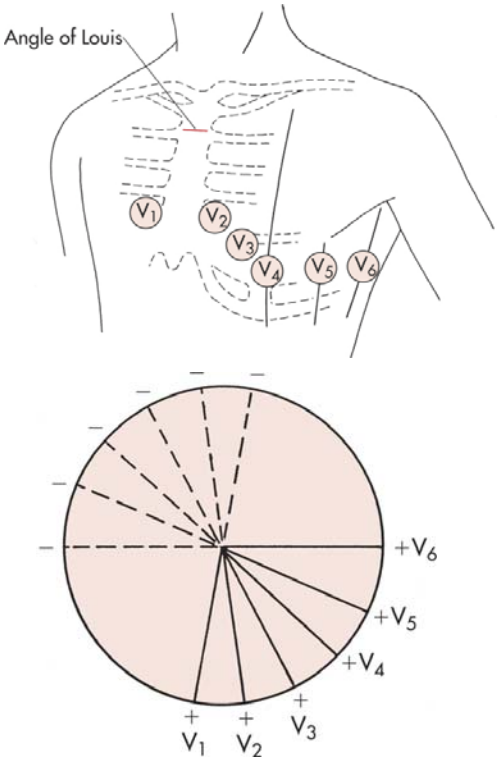


Oblique section through right and left ventricles

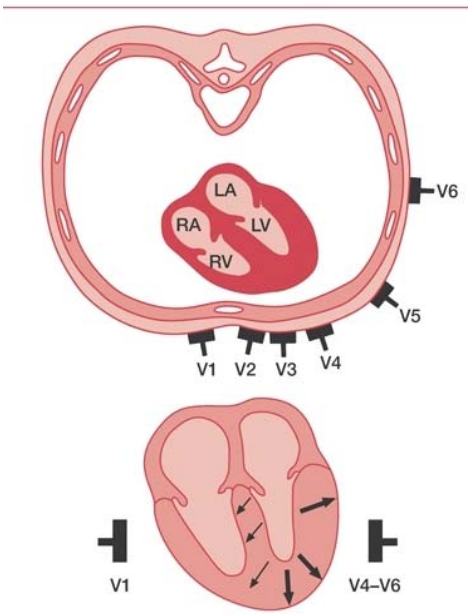
4. Orientation of leads

◦ Horizontal plane leads

Anterior Chest Leads

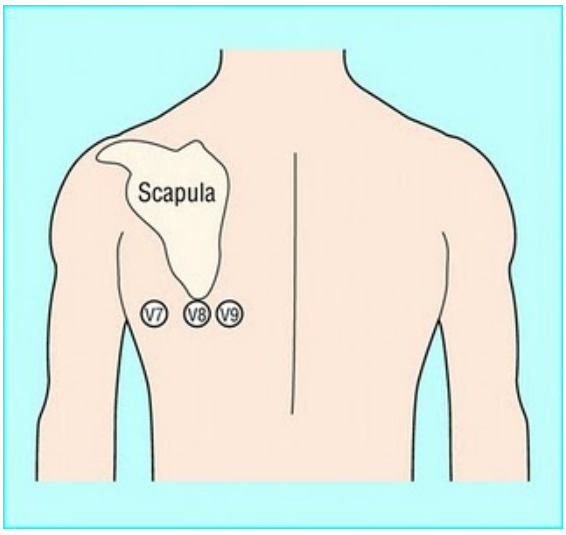


Location of the electrodes for the chest (precordial) leads

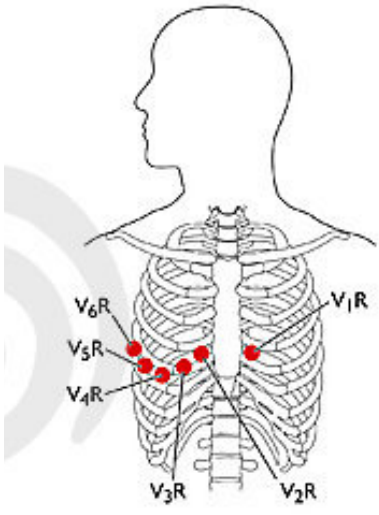


The positive poles of the precordial chest leads point anteriorly and the negatives poles point posteriorly.

Posterior Chest Leads

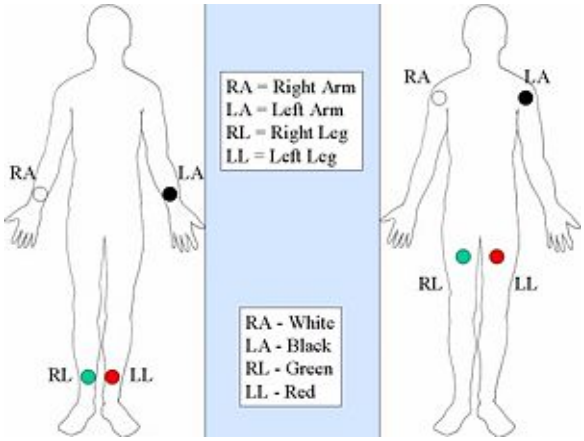


Right-sided Chest Leads



◦ **Frontal plane leads**

The Limb Leads - Standard and Augmented Leads

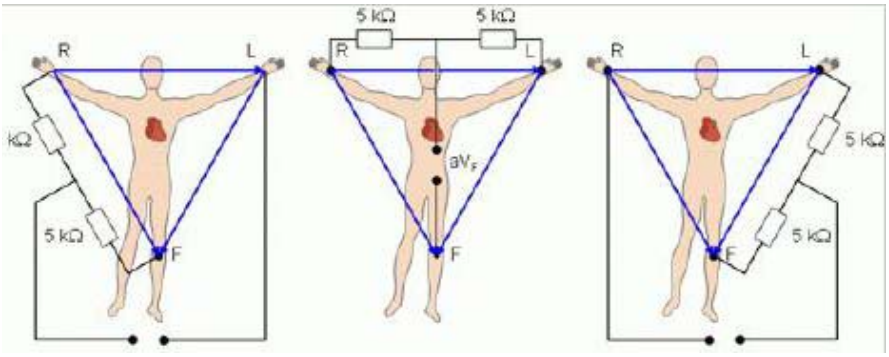


Standard Leads

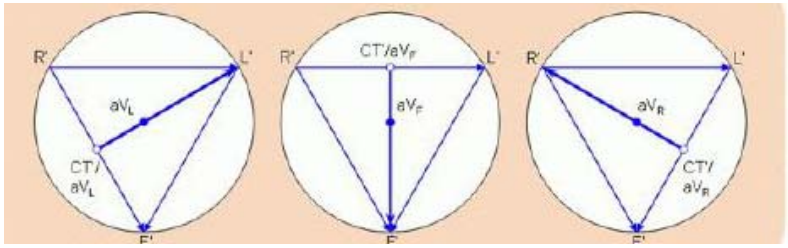
Standard lead I	RA −ve	LA +ve
Standard lead II	RA −ve	LL +ve
Standard lead III	LA −ve	LL +ve

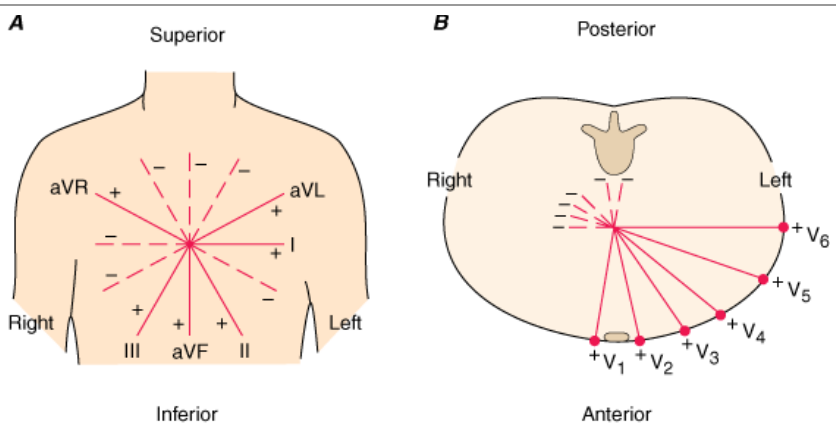
Augmented Leads

AV_L	LA +ve; RA, LL −ve
AV_F	LL +ve; RA, LA −ve
AV_R	RA +ve; LA, LL −ve



aV_L aV_F aV_R





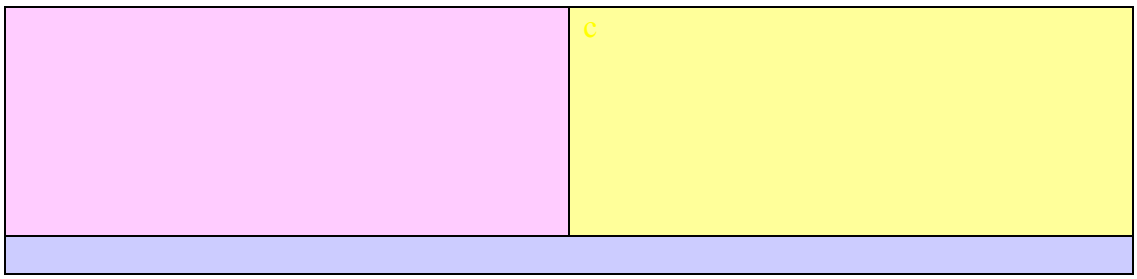
The six frontal plane (*A*) and six horizontal plane (*B*) leads provide a three-dimensional representation of cardiac electrical activity.

Areas of the myocardium viewed by specific leads

Std II, Std III, aVF	Inferior (diaphragmatic) surface of LV
Lead V1	Right ventricle Right and left atria Interventricular septum (superior aspect) Endocardial aspect of the posterior left ventricle (Thus V1 has a view of all four cardiac chambers)
Lead V2	Interventricular septum (superior aspect) Endocardial aspect of posterior left ventricle.
Lead V3	Interventricular septum (inferior aspect)
Lead V4	Interventricular septum (inferior aspect) Apex
Leads V5, V6	Lateral aspect of left ventricle (inferior aspect)
Std I, aVL	Lateral aspect of left ventricle (superior aspect)
aVR	Endocardial aspect of left ventricle

5. ECG paper

The ECG is recorded such that
- the 6 limb leads (standard & augmented) are recorded on the left (pink)
- the 6 chest (V) leads on the right (yellow)
- the rhythm strip at the bottom (blue), either Std Lead II or Lead V1.



The ECG paper consists of small squares 1mm x 1mm, and big squares 5mm x 5mm

In the horizontal plane
The value of a big square (5mm) is 0.2 seconds; a small square (1mm) is 0.04seconds.

In the vertical plane
The value of two big squares (10mm) is 1millivolt (mV), so each small square in the vertical plane is equivalent to 0.1mV

6. ECG interpretation: PQRSTU

When interpreting an ECG recording, we need to assess the following:

1. Calibration
2. Rate
3. Rhythm
4. Axis
5. P wave
6. PR interval
7. PR segment

QRS:
8. Pathological Q waves
9. Duration
10. Voltage
11. Configuration

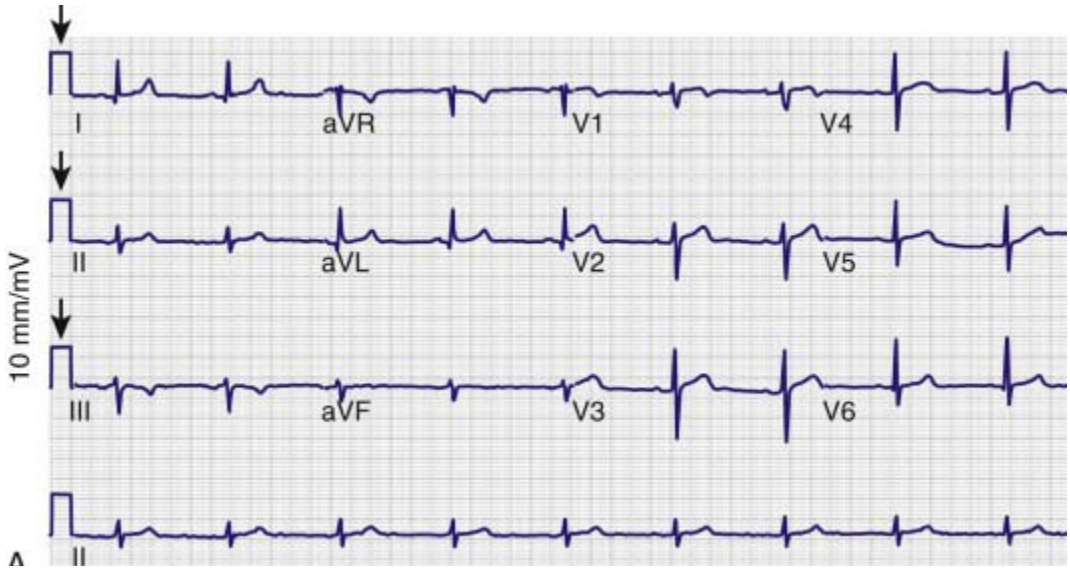
12. ST segment
13. T wave
14. QT interval
15. U wave

To group these observations another way, we need to assess:

1. Calibration
2. Rate, rhythm and axis
3. The waves – P, T and U waves (and any other waves, such as delta or J waves)
4. The QRS complexes
5. The segments – PR and ST
6. The intervals – PR and QT

.

1. Calibration The ECG is calibrated such that the 1mV standardisation mark is 10 mm tall and the horizontal line of the mark is 5mm wide (0.2 seconds) This means that the ECG is being recorded at 25mm/second



Normal 10mm/mV & 25mm/second calibration. Note the box-shaped calibration mark to the left of the complexes, two big squares tall & one big square wide

2. Rate

Normal = 60 −100 /min

Regular rhythm:
Estimate the rate by counting the number of big squares between successive R waves, and dividing this number into 300.

R – R interval of:	
1 square corresponds to a heartrate of	300/min
2 squares	150/min
3 squares	100/min
4 squares	75/min
5 squares	60/min
6 squares	50/min

Rate may also be determined by dividing number of small squares between R waves into 1500

Irregular rhythm:
Count the number of QRS complexes in 50 big squares and multiply your answer by 6 (5 big squares = 1 second, 50 big squares = 10 seconds)

3. Rhythm

Rhythm / **Sinus**
\ **Non-sinus**

Is the patient in normal sinus rhythm?

In normal sinus rhythm the following pertain:

▫ The sinus node is the pacemaker of the heart
Because of the anatomical position of the SA node in relation to the AV node, in sinus rhythm, the P wave is always +ve in Std II, and ─ve in aVR. This is because the P wave axis is directed towards the +ve pole of Std II, and away from aVR.

▫ Each P wave is followed by a QRS complex
Each atrial depolarisation wave is conducted through the AV node and results in depolarisation of the ventricles.

▫ The PR interval in a particular lead is constant (the PR interval may vary slightly from lead to lead)
In sinus rhythm, conduction through the AV node occurs at a normal, constant rate.
In normal sinus rhythm, the heart rate varies with the phases of respiration, so-called sinus arrhythmia, the rate increasing with inspiration and slowing down on expiration.

If the patient is *not* in normal sinus rhythm:

Either the SA node is still functioning as the cardiac pacemaker, but there is a partial or complete block to transmission of the depolarisation wave to the ventricles at the level of the AV node (evidence of SA node firing in the form of regular P waves is present)
or
An ectopic focus in atria, AV node or ventricles has taken over the function of cardiac pacemaker and over-ridden the SA node. This may be for a very brief period (e.g. atrial or ventricular ectopic beats) or for longer periods e.g. atrial fibrillation.

If an ectopic rhythm is evident:

- Are the QRS complexes narrow or wide?
- Is the rhythm regular or irregular?

Width (duration) of QRS complexes

Is the rhythm originating in the atria, the AV nodal tissue or the ventricles?
The QRS complexes are usually narrow when the ventricles are being activated along the normal pathway – along the bundle branches – so will be narrow when an ectopic focus is situated in atrial or nodal tissue.
If the ectopic focus is in the ventricles, the complexes generated will be wider than normal, as the ventricular tissue is activated from myocyte to myocyte, rather than via the specialised conduction tissue, so the ventricular activation takes longer.

Arrhythmias with narrow QRS complexes:
(rhythms originating in the atria or AV nodal tissue)

1. Sinus arrhythmia	**irregular**
2. Sinus rhythm with AV block	
First degree	**regular**
Second degree (Mobitz I)	**irregular**
Second degree (Mobitz I)	**irregular**
Third degree (nodal escape)	**regular**
3. Ectopic atrial or nodal rhythms	
Atrial/nodal ectopic beats	**irregular**
Supraventricular tachycardias	**regular**
Atrial flutter	**regular**
Atrial fibrillation	**irregular**

Arrhythmias with wide QRS complexes:
(rhythms originating in the ventricles)

Ventricular ectopic beats	**irregular**
Ventricular tachycardia	**regular**
Ventricular flutter	**regular**
Ventricular fibrillation`	**irregular**
Third degree AV block (ventricular escape)	**regular**

In summary, there are three causes of an irregular rhythm (sinus arrhythmia and sick sinus syndrome excluded)

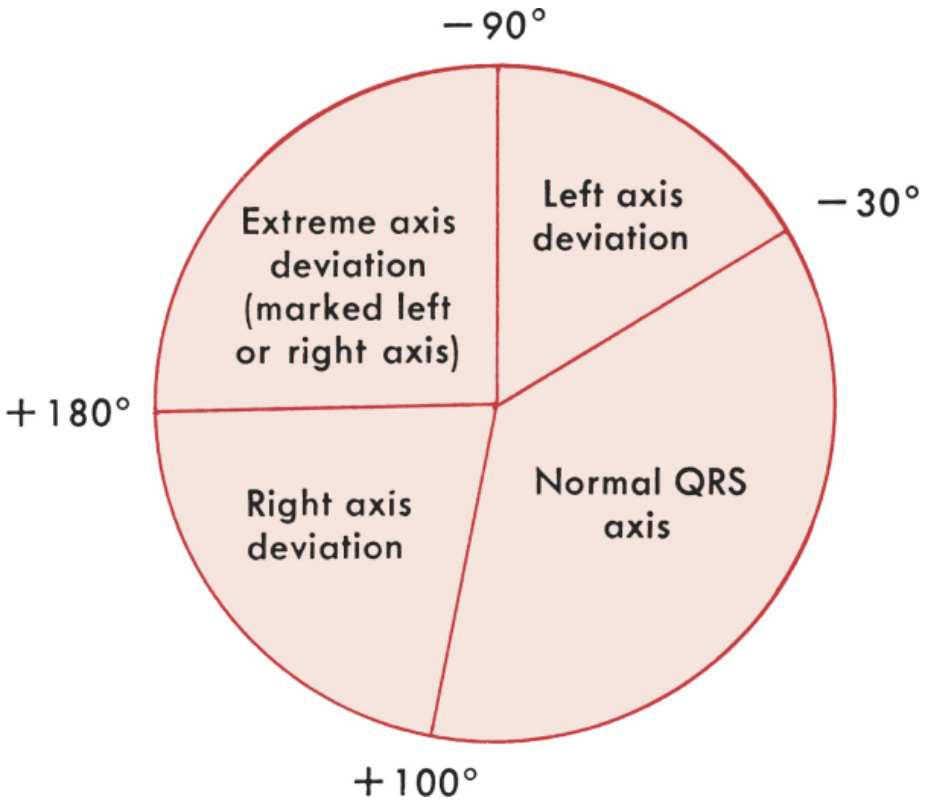
1. **Ectopic beats (atrial, nodal or ventricular)**
2. **Second degree AV block, usually Mobitz I**
3. **Atrial or ventricular fibrillation**

Escape rhythms

These occur in response to a nodal block, which necessitates that a focus distal to the block takes over the function of pacemaker for the heart.
SA node block → atrial or AV nodal escape rhythm (AV nodal rate = 40 – 60/min)
AV node block → ventricular escape rhythm (Idioventricular rate = 30 - 40/min) if block low down in AV nodal tissue; AV nodal escape rhythm if block high up in AV node.

4. Axis

The normal axis of the heart lies between −29 degrees and +100 degrees.

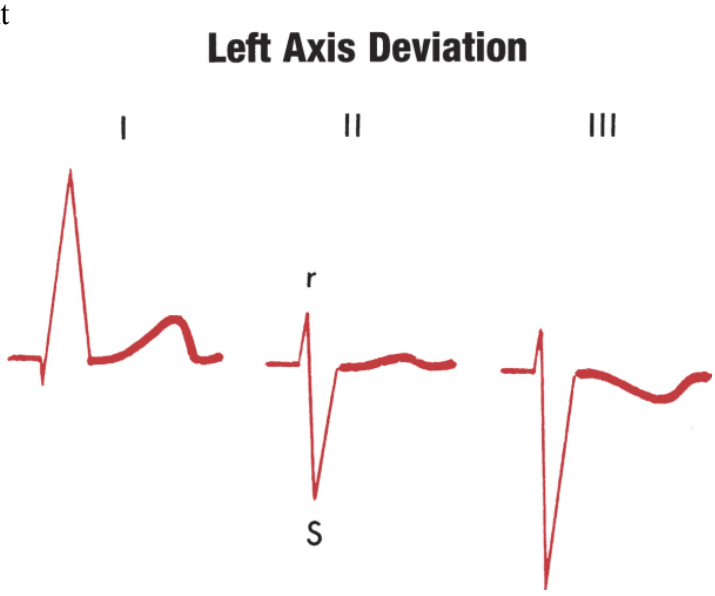


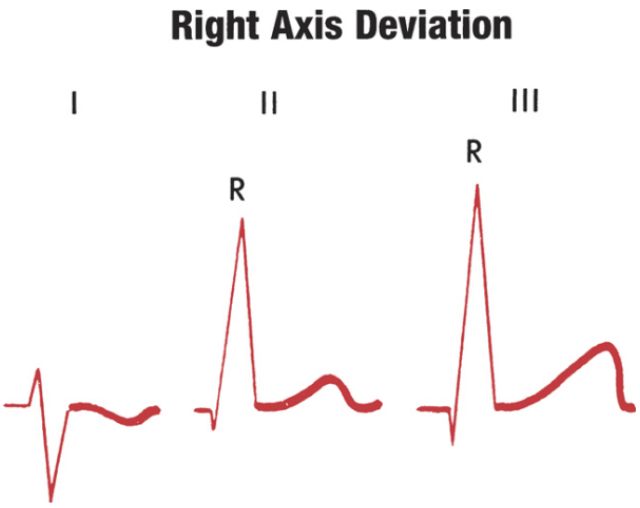
To determine the axis, the standard leads are used as per table below (blue shaded areas)

	Std I	Std II	Std III
Normal	▲	▲	▲ or ▼
LAD	▲	▼	▼
RAD	▼	▲ (occ ▼)	▲
Extreme	▼	▼	▲ or ▼

Causes of left axis deviation
(–30 º to –90 º)

1. Marked left ventricular hypertrophy
2. Left anterior hemiblock
3. Inferior MI
4. Pregnancy
5. Normal variant





Causes of right axis deviation
(+100 º to +180 º)

1. Right ventricular hypertrophy
2. Left posterior hemiblock
3. Lateral MI
4. Acute pulmonary embolism
5. Emphysema
6. Dextrocardia
7. Spurious (Left & right arms interchanged)
8 Normal variant

5. P wave

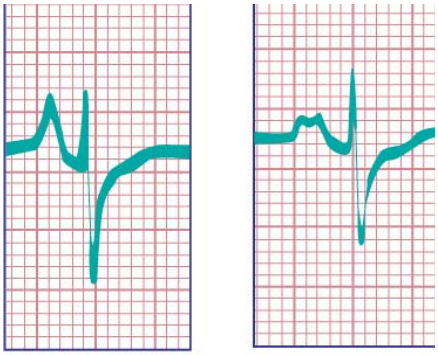
The P wave reflects depolarisation of the atria. This wave is usually a single deflection, and is a composite wave representing depolarisation of both right and left atria. When conduction through the atria is slow, the P wave may be seen as a series of two waves, the first being due to depolarisation of the right atrium, the second caused by left atrial depolarisation occurring shortly thereafter.

Height and shape of P wave

A normal P wave is < 3mm x 3mm in height and width.

Right atrial hypertrophy ("P pulmonale") = P wave ≥3 mm in *height* in limb leads (often best seen in Std lead II)

Left atrial hypertrophy ("P mitrale") = P wave ≥3 mm in *width*. The P mitrale may have a humped or bifid shape.
In left atrial hypertrophy, the P wave in lead V1 may be biphasic, with a wide or deep –ve component ≥1mm



Atrial enlargement. *A,* Peaked narrow P waves characteristic of right atrial enlargement.
B, Wide bifid M-shaped P waves typical of left atrial enlargement

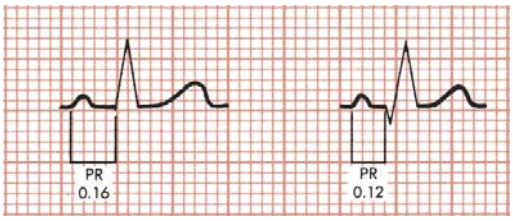
Vector of P wave

Inverted:	aVR
Upright:	I II aVF V4 – V6
Upright/biphasic/inverted:	V1 – V3 III aVL

6. PR Interval

The PR interval comprises depolarisation of the atria followed by conduction of the wave of depolarisation through the AV nodal tissue to the top of the interventricular septum.

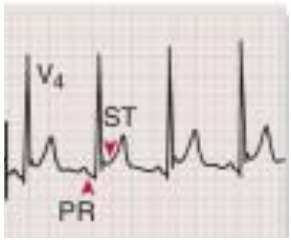
It is measured from beginning of the P wave to the beginning of the QRS complex.
Normal = 0.12 – 0.2 sec (3 – 5 small squares)
>0.2 sec = first degree heart block



Measurement of the PR interval

7. PR Segment

The PR segment reflects the time taken for transmission of the wave of depolarisation from atria to ventricles via the AV node and bundle of His.
The PR segment is normally isoelectric. Pericarditis causes depression of the PR segment



Acute pericarditis is often characterised by two apparent injury currents, one atrial, the other ventricular. The atrial injury current vector produces PR depression. The ventricular injury current is associated with ST elevation.

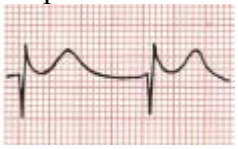
QRS Complex

The QRS complex reflects depolarisation of the ventricles. Four features of the QRS complex need to be assessed:

- **Q waves**
- **Duration**
- **Voltage**
- **Configuration**

8. Pathological Q waves

Definition: A pathological Q wave is >25% the height of the ensuing wave (from tip of Q to peak of R). Sometimes the pathological Q wave is not deep but wider than normal (>0.04sec in duration)



Example of a pathological Q wave in Std III. Note that the depth of the Q wave is > 25% the total height of the complex, from tip of Q to peak of R.

9. Duration

Normal duration is ≤ 0.10sec (2½ small squares)

10. Voltage

Criteria for normal voltage of left ventricle

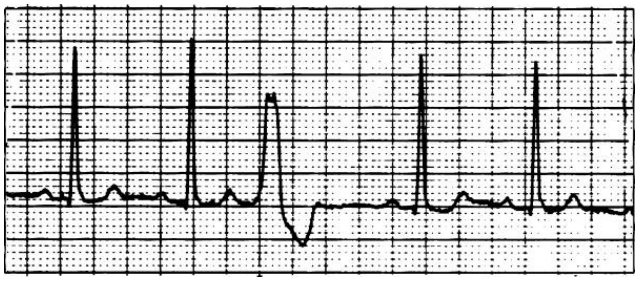
▫ Limb leads (from top of R to bottom of S):		10 – 15 mm
▫ V leads:	S in V1/V2 + R in V5/V6:	≤ 60 mm if <30 years
		≤ 40 mm if 30-40 years
		≤ 35 mm if >40 years
▫ Std I		< 15 mm
▫ aVL		< 11 mm

Criteria for normal voltage of right ventricle

▫ V1:	r < S,
▫ Axis	No right axis deviation

11. Configuration

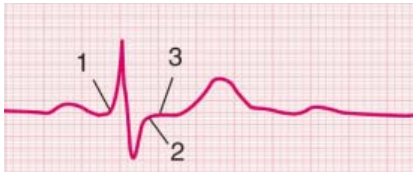
◦ Presence of abnormal waves:
  Delta waves of Wolff-Parkinson-White syndrome
  J waves of hypothermia
  R waves too big in V1 (R>s) or
  R waves too small in V3 (r < 3mm)
◦ Presence of VPBs



Ventricular premature beat (VPB) showing distortion of the QRS and T wave inversion, absence of P wave and compensatory pause before next sinus beat appears.

12. ST Segment

The ST segment commences at the J point (the junction of the ST segment and the QRS complex) and extends to the beginning of the T wave. Should be isoelectric as there is no voltage difference between areas of the ventricles in this phase of the ECG.



Lead V_5.
1 = PQ junction that serves as the baseline reference
2 = J point
3 = ST segment
In this example, slight ST depression is present.(2 should be at same level as 1)

13. T wave

The T wave represents ventricular repolarisation.

Vector

Its vector is often the same as the preceding QRS complex.
Always inverted in aVR
Upright or inverted in V1,V2 (in young people), Std III
Upright in all other leads.

Height

Its height is dependent on the height of the preceding QRS complex, but as a rough guide, should be ≤ 5 mm in limb leads and ≤ 10mm in chest leads.

14. QT Interval

Encompasses ventricular de- & repolarisation. It is measured from beginning of QRS to end of T wave. The QT interval is dependent on heart rate, decreasing as rate increases, and becoming longer as rate slows. As a rough guide, the QT interval should normally be < half the R-R interval.
Corrected QT is the QT calculated for a heart rate of 60 bpm.

QTc = QT/√R-R (seconds)

Corrected QT in males is 0.43 sec, in females 0.45 sec.

15. U wave

The U wave is a small wave (≤ 25% the height of the T wave) which follows the T wave and which is thought to represent repolarisation of the Purkinje fibers. It is often only visible at slow heart rates, and is most prominent in the right sided chest leads.

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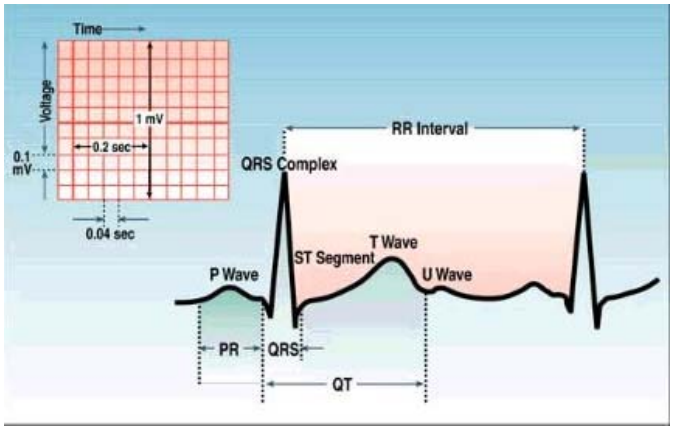


DIRECTION of P and T WAVES

The P wave

< 0.12 sec (< 3 small squares)

≤ 3mm height (≤3 small squares)

Inverted in aVR (all deflections are always negative in this lead)

Upright/biphasic/inverted V1 – V3, III, aVL

Upright I, II, aVF, V4 – V6

The T wave

<5 mm height in limb leads

<10 mm in praecordial leads

Inverted in aVR

Upright or inverted in V1, V2 (young people), III

Upright in all other leads.

Easy way to remember: in Leads V1 and V2

- P and T waves may be upright or inverted (especially in young people)
- ↑ST segment may be a normal variant (<3mm) - "early repolarisation" pattern
- ↓ST segment may be a normal variant (<1mm)

*Important always to take note of the history, and to compare current ECG with previous ECGs. If ST deviation from isoelectric line is not present in previous ECGs, the elevation or depression is likely to be significant.

Pathological T waves

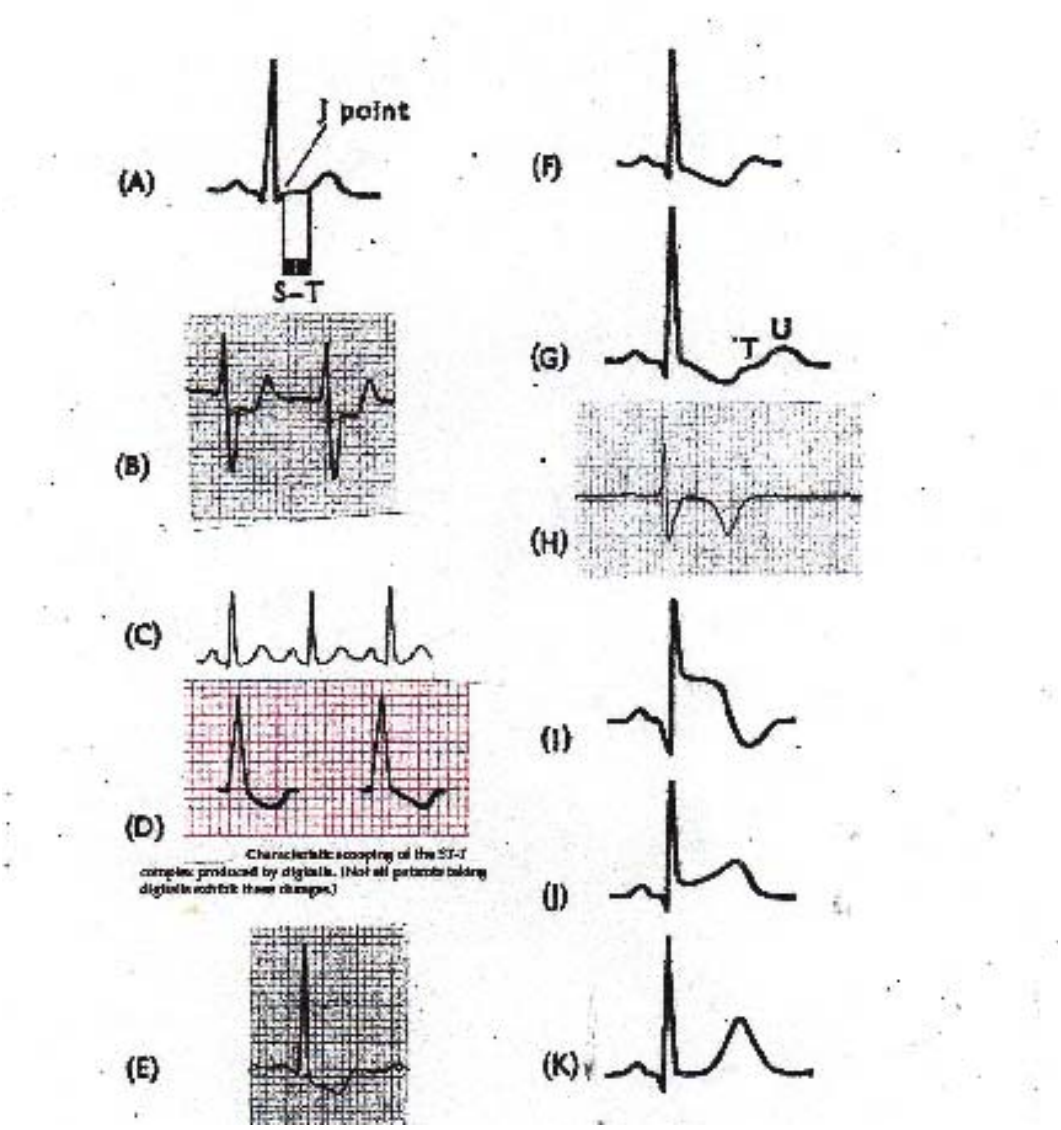
Tall T waves (>10 mm in V leads / >5mm in limb leads)

- Ischaemic causes:
  - Acute transmural MI - "hyperacute T waves"
  - Coronary artery spasm - Prinzmetal's Angina / Cocaine
- Non- Ischaemic causes:
  - Hyperkalaemia
  - Acute pericarditis

Inverted T waves

Myocardial ischaemia/infarction
Ventricular hypertrophy
BBB
Pulmonary embolism
Cardiomyopathy (CMO)
Digoxin
CVA

Normal and Abnormal ST Segments and T Waves



A. Normal ST segment with J point
B. Horizontal ST depression in myocardial ischaemia
C. ST segment sloping upwards in sinus tachycardia
D. ST sagging in digoxin therapy
E. Asymmetrical T wave inversion associated with ventricular hypertrophy
F. Similar pattern sometimes seen without voltage changes of hypertrophy – so-called "strain"
G. ST sagging and prominent U waves in hypokalaemia
H. Symmetrical T wave inversion of myocardial ischaemia or infarction
I. ST elevation in acute myocardial infarction
J. ST elevation in acute pericarditis
K. Peaked T wave in hyperkalaemia

ECG Differential Diagnoses

P waves

- **Tall P waves**
  P wave ≥3 mm in height in limb leads ("P pulmonale")
  - Right atrial hypertrophy

- **Wide P waves**
  P wave ≥3 mm in width in limb leads ("P mitrale")
  - Left atrial hypertrophy
  - Slow atrial conduction due to IHD

- **P wave with altered configuration**
  P wave in sinus rhythm is always −ve in aVR, +ve in Std II.
  If pacemaker of the heart is a focus low down in the atrium or in AV nodal tissue, P wave will be +ve in aVR and −ve in Std II

  The P wave of an atrial ectopic beat close to the SA node has a slightly different configuration from the sinus P wave.

PR Duration

Short PR
Accessory pathways such as W-P-W
Nodal tachycardia (atria depolarised just before ventricles)
Ectopic atrial rhythm (focus close to AV node)

Long PR
Elderly
Drugs "ABCD" e.g. Adenosine, Beta blockers, Calcium channel blockers, Digoxin
Myocarditis
IHD especially involvement of RCA which supplies AV node in 90% of individuals. AV block is common in inferior myocardial infarction, when caused by RCA occlusion

QRS Complex

Pathological Q waves

Normal variant in aVR, aVL, aVF, Std III, V1
Myocardial infarction (transmural)

Left ventricular hypertrophy	Absent r waves V1 – V3 → QS waves in these leads
Right ventricular hypertrophy	Poor/ reversed r wave progression may → QS waves in right-sided chest leads
Left bundle branch block.	Absent r waves V1 – V3 → QS waves in these leads
HOCM	Septal hypertrophy → deep Q waves in lateral chest leads (Leads V5 & V6)

Widened QRS complex (> 0.10sec)

Bundle branch block (left or right)
Non-specific intraventricular conduction delay
Ventricular beats
Hyperkalaemia
Drugs e.g. tricyclics
W-P-W

Low voltage QRS complexes
(<5mm limb leads, <10mm chest leads)

Spurious (ECG calibration altered to 5mm/mV)
COPD
Obesity
Pericardial effusion
Infiltration of the myocardium e.g. hypothyroidism/amyloid
Extensive myocardial infarction

R wave > s wave in Lead V1

Posterior MI (transmural)
Right ventricular hypertrophy
Right bundle branch block
W-P-W

R wave in Lead V3 < 3 mm ("poor R wave progression")

Anteroseptal MI
LVH/RVH
LBBB
COPD

ST segment elevation

Transmural myocardial infarction (STEMI)
Coronary artery spasm: Prinzmetal's angina
Cocaine
Ventricular aneurysm
Normal variant (V1 – V2, ≤ 3 mm)
LVH (V1 – V3)
LBBB (V1 – V3)
Acute pericarditis
Acute myocarditis
Hyperkalaemia

ST segment depression

Myocardial ischaemia: · angina pectoris
· sub-endocardial MI
Reciprocal change in acute transmural myocardial infarction
Normal variant (only in V1 – V2, < 1 mm)
Left ventricular hypertrophy (in left chest leads, V5-V6)
Right ventricular hypertrophy (in right chest leads, V1-V2)
LBBB (V5 –V6)
RBBB (V1-V2)
Digoxin
Hypokalaemia

T wave abnormalities

Tall T waves (> 10 mm in V leads/> 5 mm in limb leads)

Acute transmural MI
Coronary artery spasm
Acute pericarditis
Hyperkalaemia

Inverted T waves

Myocardial ischaemia/infarction
Ventricular hypertrophy
BBB
CMO
Digoxin
CVA
Acute pulmonary embolism (Leads V1 – V4)
(Hypokalaemia →T wave flattening)

QT Interval

Short QT
Congenital
Drugs e.g. digoxin

Hyperkalaemia
Hypercalcaemia
Hyperthermia
Acidosis

Long QT
Congenital
Drugs e.g. Amiodarone
Erythromycin
Hypokalaemia
Hypocalcaemia
Hypothermia

IHD
Myocarditis
Head injury/Sub-arachnoid Hx/Vasovagal

U Waves

Prominent U waves
Hypokalaemia
Antiarrhythmic drugs e.g. Amiodarone
LVH
Sub-arachnoid Hx

Inverted U waves
Myocardial ischaemia

Axis Deviation

LAD
LVH
Left anterior fascicular block
Inferior MI
Pregnancy
Normal variant

RAD
RVH
Left posterior fascicular block
Lateral MI
Acute pulmonary embolism
COPD
Dextrocardia
Normal variant
Spurious (arm electrodes interchanged)

Classification of arrhythmias

Arrhythmias arise due either to a disorder of impulse

- **formation**

or

- **conduction**

Disorders of impulse formation

In addition to the specialised tissue known as the sinu-atrial node (SA node), which normally fills the role of pacemaker for the heart, all elements of the conducting tissue, such as the atrio-ventricular node (AV node), bundle branches and Purkinje fibers are capable of performing this pacemaker function, as well as the cardiac myocytes, which all have inherent rhythmicity – the ability to generate an impulse de novo.

An arrhythmia is any rhythm which does not fulfil the criteria for normal sinus rhythm (the impulses originate in the SA node at a rate of 60 -100 times per minute, each impulse is conducted through the AV node to the ventricles and the time taken for this to occur is the same for each impulse generated)

Arrhythmias may therefore arise in the SA node, the atria, the AV node, or the ventricles.

- **Sinus node**

  Sinus arrhythmia

  Sinus bradycardia

  Sinus tachycardia

- **Atria**

  Atrial extrasystoles

  Paroxysmal atrial tachycardia*

  Atrial flutter

  Atrial fibrillation

- **AV node**

  AV nodal extrasystoles

  AV nodal re-entrant tachycardia*

- **Ventricles**

  Ventricular extrasystoles

  Ventricular tachycardia

  Ventricular flutter

  Ventricular fibrillation

Disorders of impulse conduction

- **SA node block**
- **AV node block** First degree

  Second degree (Mobitz I or Mobitz II)

  Third degree (complete heart block)
- **Accessory pathways e.g. Wolff-Parkinson-White syndrome** → re-entrant tachycardia *

* Supra-ventricular tachycardias (SVTs)

Escape Rhythms

A focus in the atria, AV node or ventricle will start to generate impulses if the impulse generating mechanism of the heart fails, and the focus then becomes the pacemaker of the heart for as long as it is the primary impulse generator. The location of the escape rhythm is dependent on the level of the defect. These rhythms are termed escape rhythms and provide a safety net for the heart in times of a block in transmission of the cardiac impulse.

SA node block (caused by, for example, inhibition of the SA node by beta blockers) will result in an **atrial escape rhythm** or one originating lower down in the AV node **(nodal escape rhythm)**

AV node block, if third degree, will result in a **nodal escape rhythm** if the block is proximal in the AV nodal tissue (sufficient normal AV nodal tissue distal to the block to generate impulses and take over pacemaker function)

or

in a **ventricular escape rhythm** if the block is distal in the AV nodal tissue (no normally functioning AV nodal tissue to take over the function of pacemaker)

Nodal escape rhythms may be differentiated (for the most part) from ventricular escape rhythms by:

- **Duration of the QRS complexes** (narrow, normal appearing QRS complexes in AV nodal escape rhythms, wide complexes in ventricular escape rhythms, because ventricles being activated from cell to cell, not along normal efficient conducting pathways, so activation takes longer)
- **Rate of the escape rhythm**

AV nodal escape rhythm rate 40 – 60 per minute

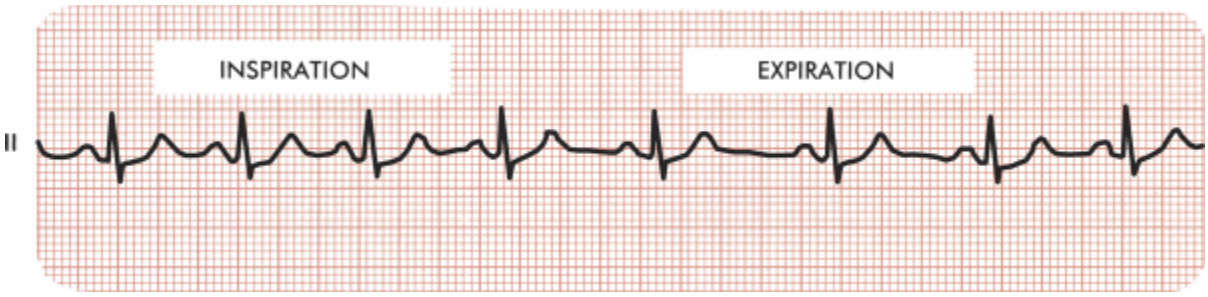
Ventricular escape rhythm rate 15 - 40 per minute (however, sometimes accelerated to >40/minute)

Arrhythmias affecting the sinus node

Sinus Arrhythmia

In healthy people, especially younger subjects, the SA node does not pace the heart at a perfectly regular rate. Instead, a slight beat-to–beat variation is present. When this variability is more accentuated, the term *sinus arrhythmia* is used.

The most common cause of sinus arrhythmia is respiration. Respiratory sinus arrhythmia is a normal finding and may be quite marked particularly in children and young adults. The heart rate normally increases with inspiration and decreases with expiration because of changes in vagal tone that occur during the different phases of respiration.



Respiratory sinus arrhythmia.

Sinus bradycardia

With sinus bradycardia, sinus rhythm is present; the heart **rate is less than 60 beats/min**.

This arrhythmia commonly occurs in the following conditions:

- Normal variant (Many people have a resting pulse rate of less than 60 beats/min, and trained athletes may have a resting or sleeping pulse rate as low as 35 beats/min.)
- Drugs that ▫ increase vagal tone (e.g., digitalis)
  ▫ decrease sympathetic tone (e.g., beta blockers)
  ▫ calcium channel blockers
- Hypothyroidism
- Hyperkalaemia
- Sick sinus syndrome (Some patients, particularly elderly ones, have marked sinus bradycardia without obvious cause, probably from degenerative disease of the SA node or surrounding tissue.)
- Sleep apnoea syndromes
- Carotid sinus hypersensitivity
- Vasovagal reactions

Sinus Tachycardia

In general, sinus tachycardia occurs with any condition that produces an *increase* in sympathetic tone or a *decrease* in vagal tone.

Rate 100 – 200 bpm (young)
100 – 150 bpm (elderly >70 years)

The following conditions are commonly associated with sinus tachycardia:

- Anxiety, excitement, exertion, and pain
- Drugs that increase sympathetic tone (e.g., epinephrine, dopamine, tricyclic antidepressants and cocaine)
- Drugs that block vagal tone (e.g., atropine)
- Fever, many infections, and septic shock
- Congestive heart failure (CHF)
- Pulmonary embolism
  Sinus tachycardia is one of the most common arrhythmias which occurs in acute pulmonary embolism.
- Acute myocardial infarction; sinus tachycardia generally a bad prognostic sign and implies extensive heart damage.
- Hyperthyroidism (sinus tachycardia at rest may be an important diagnostic clue)
- Phaeochromocytoma
- Intravascular volume loss because of bleeding, vomiting, diarrhoea, acute pancreatitis, dehydration.
- Alcohol intoxication or withdrawal

Ectopic arrhythmias originating above the ventricles

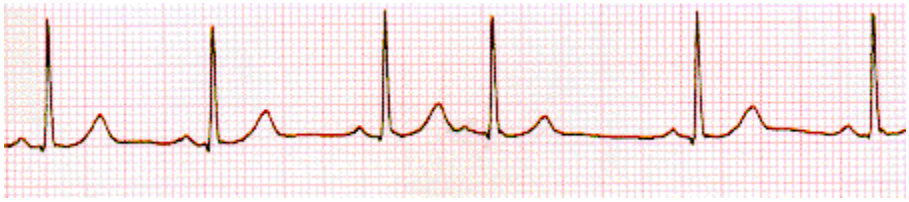
- **Atrial premature beats**
- **Supraventricular tachycardias**
- **Atrial Flutter**
- **Atrial Fibrillation**

Atrial premature beats (APBs)

An ectopic focus in left or right atrium discharges and depolarises the atria before the sinus node was due to fire again.

Aetiology

Normal hearts (APBs are the most common arrhythmia)
Emotional stress
Caffeine excess
Drugs e.g. those used for asthma, such as epinephrine, aminophylline
Hyperthyroidism
Structural heart disease e.g. valvular lesions

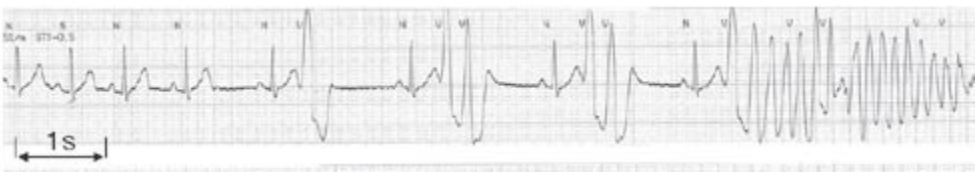


The fourth complex in this recording is an atrial premature complex.

Note the following:

▫ configuration of the ectopic P wave is slightly different from that of the sinus P waves
▫ narrow, normal appearing QRS complex follows the ectopic P wave
▫ short R-R interval preceding the complex
▫ long R-R interval following the complex, the so-called "compensatory pause"

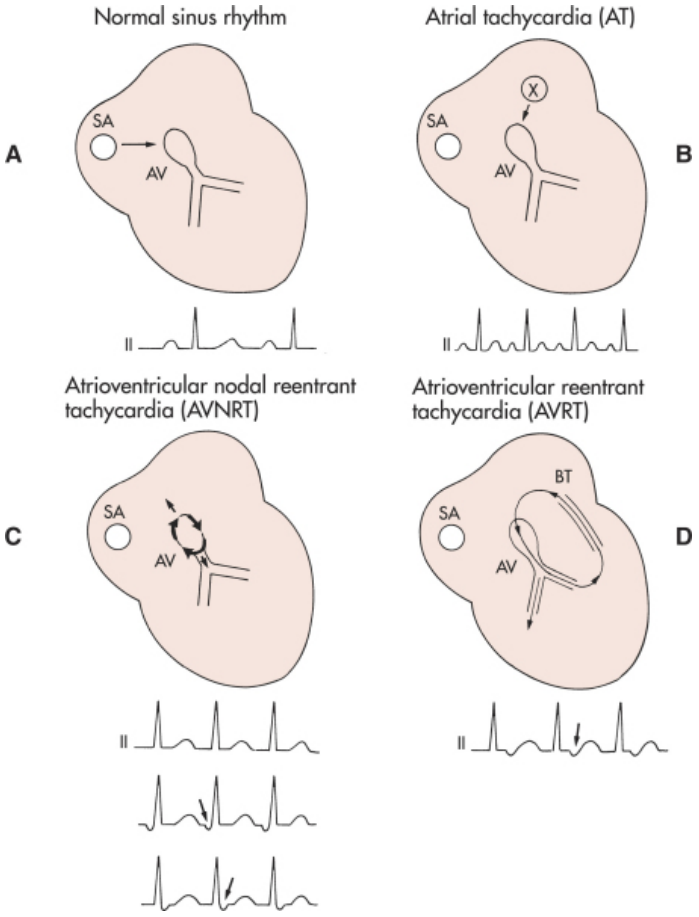
The APB is distinguishable from a VPB (ventricular premature complex) by:
▪ no discernible P wave precedes the VPB
▪ the VPB differs obviously in configuration from the normal QRS complexes, being prolonged in duration (wide), often bizarre looking and followed by T wave inversion.



The 6th, 8th, 9th11th, 12th complexes are VPBs; after the 13th complex (normal QRS) an episode of VT has commenced.

Supraventricular tachycardias *Rate ≤ 250 bpm*

- **Atrial tachycardia** (≥ 3 consecutive APBs) – P wave *before* QRS (usually +ve in Std II) or buried in preceding T wave
- **Nodal re-entrant tachycardia** – P wave often *hidden in QRS*, may be just before/after QRS, when it will be seen to be –ve in Std II (atria and ventricles being depolarised at approximately the same time)
- **Bypass tract re-entrant tachycardia –** ventricles activated before atria, therefore P wave occurs *after* QRS and _ve in Std II

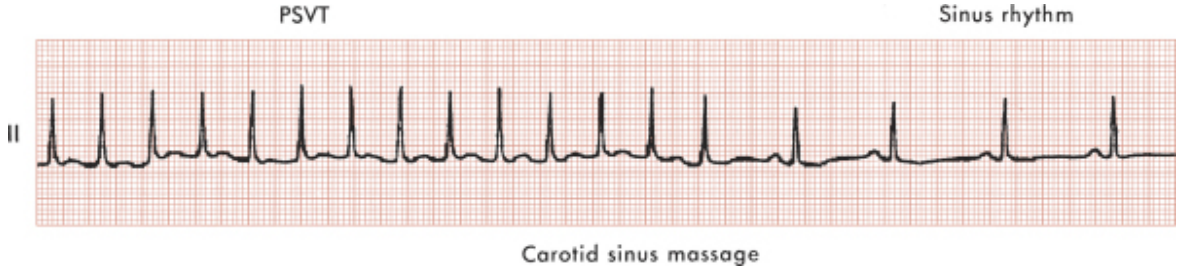


A, Normal sinus rhythm.

B, With atrial tachycardia (AT), a focus *(X)* outside the sinoatrial node fires off automatically at a rapid rate.

C, With atrioventricular (AV) nodal reentrant tachycardia (AVNRT), the cardiac stimulus originates as a wave of excitation that spins around the AV nodal (junctional) area. As a result, retrograde P waves may be buried in the QRS or appear immediately before or just after the QRS complex *(arrows)* because of nearly simultaneous activation of the atria and ventricles.

D, A similar type of reentrant (circus-movement) mechanism may occur with a bypass tract (BT) of the type found in Wolff-Parkinson-White syndrome (see). This mechanism is referred to as *atrioventricular re-entrant tachycardia* (AVRT). Note the negative P wave *(arrow)* in lead II, somewhat after the QRS complex.



Paroxysmal supraventricular tachycardia (PSVT) treated with carotid sinus massage. The first 14 beats in this rhythm strip show the regular tachyarrhythmia with a rate of about 140 beats/min and no visible P waves.

Atrial Flutter *Rate: 250 – 350 per minute (average 300)*

Re-entrant tachycardia travelling anti-clockwise in right atrium (80%), clockwise (20%). Route is around the tricuspid valve, inbetween the vena caval orifices.
Seen as a sawtooth appearance in inferior leads.
A regular atrial tachycardia and therefore usually a regular ventricular rhythm as well; sometimes if there is impairment of conduction through the AV node by disease or drugs, the ventricular response will be irregular depending on how variable the atrio-ventricular block is e.g. varying between 2:1, 3:1, 4:1 block etc.

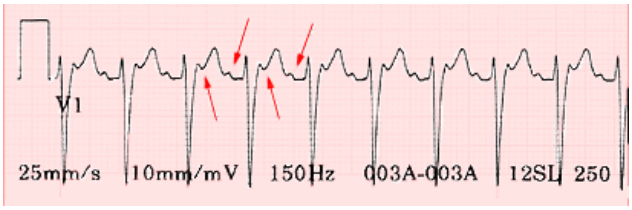
Causes:

Usually occurs only in a diseased heart:	Mitral valve disease
	Ischaemic heart disease
	Cardiomyopathy
	Hypertension
Or, secondary to:	Chronic obstructive pulmonary disease (COPD)
	Pulmonary embolism
	As a complication of cardiac surgery

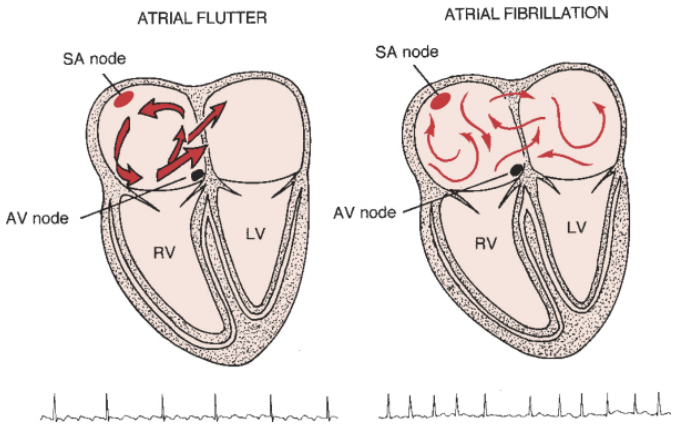
Atrial rate often 300 pm, with a physiological AV block → 2:1 conduction, so ventricular rate = 150 bpm. Conduction block may increase to 3:1 → ventricular rate = 100 bpm.; 4:1 → ventricular rate = 75 bpm. (AV node cannot normally conduct impulses faster than 200 per minute)

Treatment:

1. Anticoagulation
2. Slow conduction through AV node with β blocker, Calcium channel blocker or Digoxin.
(β blockers inhibit sympathetic tone of AV node, Digoxin enhances parasympathetic tone of AV node, Ca channel blockers directly inhibit impulse conduction by impairing cellular entry of Calcium ions)
3. Antiarrhythmic agents, such as Amiodarone
4. DC cardioversion
5. Radiofrequency ablation of tract
6. Atrial pacemaker



The arrows are directed at the flutter waves; this patient has a physiological 2:1 AV block (every 2nd flutter wave is blocked at the AV node, as it is still in its refractory period, having just conducted the previous flutter wave to the ventricles)



Comparison of mechanisms of atrial flutter and atrial fibrillation (AF). Atrial flutter is typically due to a large reentrant wave originating in the right atrium. With typical atrial flutter, the wave spreads in counterclockwise direction. AF is attributed to either multiple reentrant wavelets and/or to multiple sites of atrial automaticity.

Atrial Fibrillation

Atrial Rate:	**350 – 600 per minute**
Ventricular Rate:	**110 – 180 per minute**

Caused by multiple re-entry circuits or multiple ectopic foci of atrial automaticity.
This is one of the most common arrhythmias, the incidence increasing with age.

Incidence
0.9% overall
4% >65 years
9% >80 years

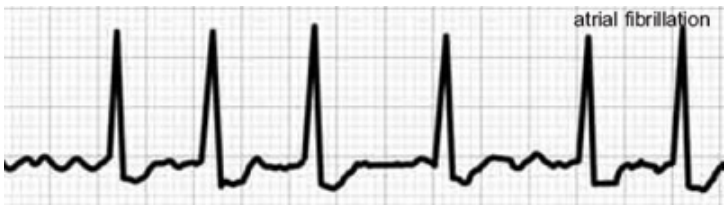
Hallmarks: No recognisable P waves, very irregular ventricular response.

Causes

Hypertension	(most common cause of AF)
Mitral valve disease	
Ischaemic heart disease	(AF occurs in 13.7% cases of acute MI)
Cardiomyopathy	
Thyrotoxicosis	
Chronic obstructive pulmonary disease	
Pulmonary embolism	
Complication of cardiac surgery	
Part of sick sinus syndrome ("tachy-brady" syndrome)	
Pericarditis (especially chronic pericarditis)	
Obstructive sleep apnoea	
Congenital heart defects e.g. ASD	
Alcohol - acute or chronic excessive intake; alcohol withdrawal syndrome	
Acute hypoxia, hypercarbia, metabolic disturbance	
Obesity	
"Lone fibrillator"	(specific foci of tissue in left atrium usually situated at the ostia of the pulmonary veins whose discharge → AF)

Treatment:

1. Pharmacological treatment and anticoagulation
2. Direct Current cardioversion.
3. RF ablation of tissue around pulmonary veins, where ectopic foci are often found.
4. Ablation of AV node with insertion of a ventricular pacemaker.
5. Atrial defibrillator



The fibrillation waves are discernible, but no discreet P waves are present. The fibrillation waves are conducted to the ventricles at random intervals, resulting in irregular production of the QRS complexes.

VENTRICULAR ARRHYTHMIAS

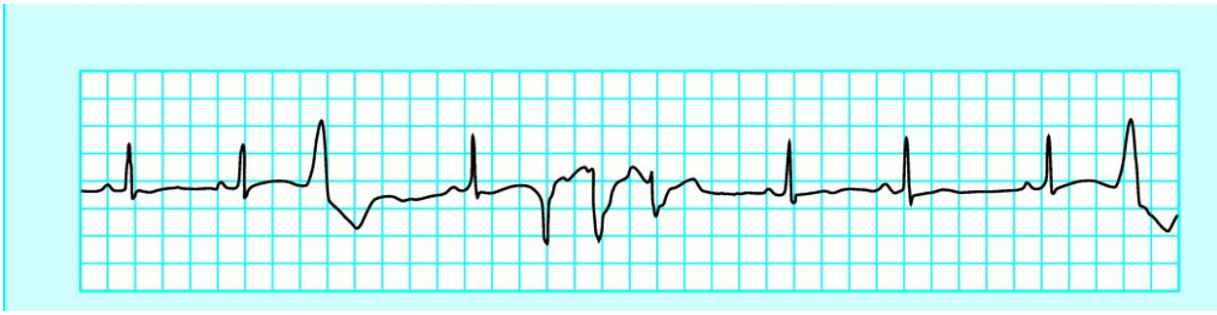
Ventricular Premature Beats (VPBs)

Aetiology

Normal hearts, particularly the elderly
Anxiety
Caffeine excess
Drugs:
- Drugs used for asthma e.g. epinephrine, aminophylline
- Digoxin (very commonly seen in digoxin toxicity)

Electrolyte disturbances
- ↓K+
- ↓Mg++

Lung disease
Hypoxia
Mitral valve prolapse
Other valvular lesions
Hypertension
IHD, particularly acute MI (most common arrhythmia in this situation)



In this rhythm strip, the third complex and the last are VPBs (occurring before the next sinus P wave was due, no preceding P wave; wide, bizarre appearing complexes, T wave inversion) in the middle is a short run of ventricular tachycardia.

Ventricular Tachycardia (VT)

VT is defined as a run of three or more consecutive VPBs.

VT may be non-sustained (lasting from three beats to 30 sec) or sustained, lasting >30 sec

Its morphology may be monomorphic or polymorphic, depending on whether consecutive VPBs have the same or a variable appearance in a single lead.

Sustained VT (VT lasting longer than 30 sec) is usually a life-threatening arrhythmia for two reasons:

1. Most patients are not able to maintain an adequate blood pressure at very rapid ventricular rates and become hypotensive.
2. The condition may degenerate into VF, causing cardiac arrest.

Very rapid VT (>300 bpm) with a sine-wave appearance is sometimes referred to as *ventricular flutter*. This arrhythmia often leads to cardiac arrest with VF

:

Causes

Sustained VT, (rate 100 – 300/minute) which may lead to syncope or sudden death, rarely occurs in patients without underlying structural heart disease. Most patients with this type of arrhythmia have some basic structural cardiac abnormality, such as::

· prior MI causing a myocardial scar (most common cause)

· cardiomyopathy

· valvular disease associated with fibrosis

· ventricular enlargement.

Treatment

Despite pharmacologic therapy, some patients are at high risk for life-threatening recurrences of sustained VT or VF. For these patients, a special device called an *implantable cardioverter defibrillator (ICD)* has been developed to deliver an internal electric shock directly to the heart during a life-threatening tachycardia

(According to Australian cardiologists, ICD also may stand for "implantable cardiac device").

Polymorphic VT (Torsades des pointes)

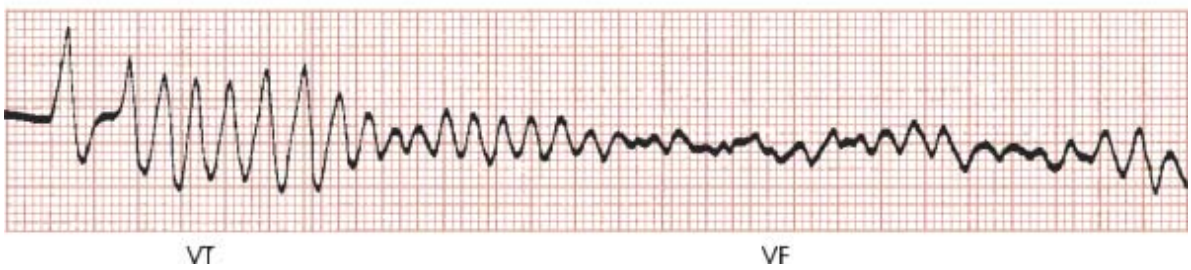
Occurs with or without a prolonged QT syndrome, for example with acute ischaemia

Ventricular Fibrillation

Aetiology

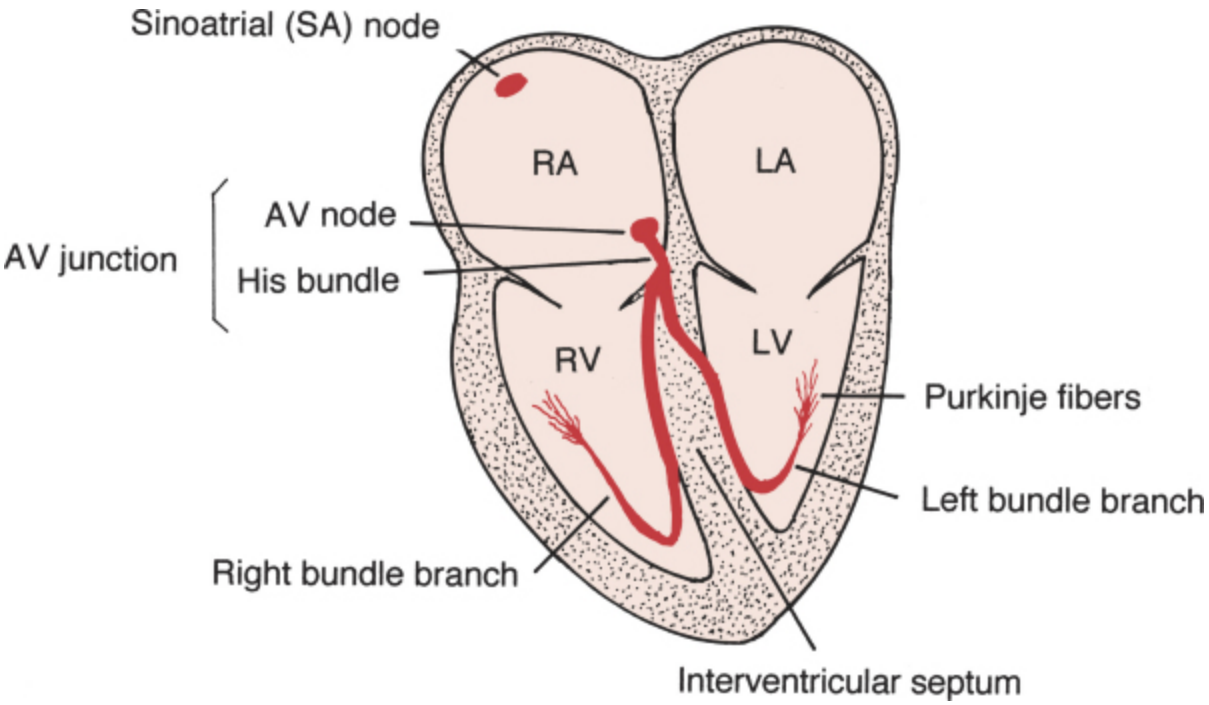
Heart disease of any type
Acute MI
Drugs
- ▫ Digoxin in toxic doses, particularly in presence of ↓K+ or ↓Mg+ +
- ▫ Epinephrine
- ▫ Drugs → ↑QT — e.g. quinidine, procainamide, erythromycin
- ▫ "Recreational" drugs — e.g cocaine

Preceding ventricular arrhythmias — e.g .ventricular premature beats or ventricular tachycardia
Short/long QT interval
Prominent U waves
Non-penetrating blow to the chest
Electric shock/lightning strike
AF occurring in a patient with W-P-W syndrome.

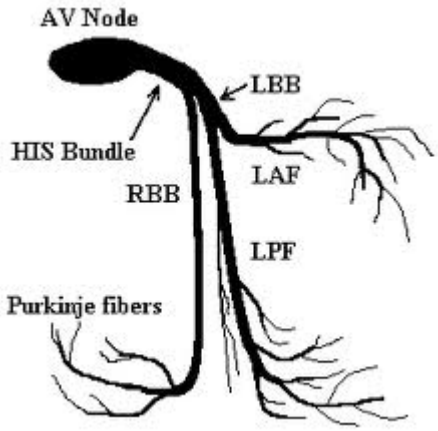


Ventricular tachycardia (VT) and ventricular fibrillation (VF) recorded during the onset of cardiac arrest. The rapid sine-wave type of VT seen here is sometimes referred to as *ventricular flutter*.

The conducting system of the heart



Normally, the cardiac stimulus is generated in the *sinoatrial (SA) node,* which is located in the *right atrium (RA).* The stimulus then spreads through the *RA* and to the *left atrium (LA) via an inter-atrial conducting pathway.* It reaches the *atrioventricular (AV)* node via three inter-nodal pathways and spreads through the AV node and the *bundle of His,* which comprise the *AV junction.* The stimulus then passes into the *left* and *right ventricles* (*LV* and *RV*) by way of the two fascicles of the *left* bundle branch and the *right bundle branch,* which are continuations of the bundle of His. Finally, the cardiac stimulus spreads to the ventricular muscle cells through the *Purkinje fibers*



LBB = Left bundle branch
LAF = Left anterior fascicle
LPF = Left posterior fascicle

Diagram showing anterior and posterior fascicles of left bundle branch

SINUS ARREST or BLOCK (SA BLOCK)

SA block or arrest can occur in the sick sinus syndrome or be caused by numerous *acute* factors, including:

- Hypoxia
- Myocardial ischaemia or infarction
- Hyperkalaemia
- Digitalis toxicity
- Toxic responses to drugs such as beta blockers and calcium channel blockers
- Vagal hyperreactivity (e.g. severe vasovagal episode)

ATRIOVENTRICULAR BLOCK (AV BLOCK)

This is characterised by a delay or interruption in conduction of the atrial impulse through the A – V conducting system, that is, the A – V node and Bundle of His

There are 3 degrees:

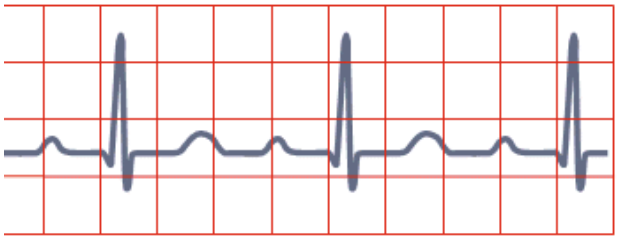
1. First degree A – V block - a *delay* in conduction
2. Second degree A – V block - *intermittent interruption* in conduction
3. Third degree A – V block - *complete interruption* in conduction

First Degree A – V block

Prolongation of the PR interval beyond 0.2 seconds. Conduction from SA node to AV node takes 0.03 sec, the remainder of the PR interval being taken up by conduction through the AV node, Bundle of His, bundle branches, Purkinje fibres. In first degree block, the delay is usually located in the A-V node.

Causes:

Old age
Ischaemic heart disease
Myocarditis e.g. acute rheumatic carditis
Drugs e.g. digoxin, beta-blockers

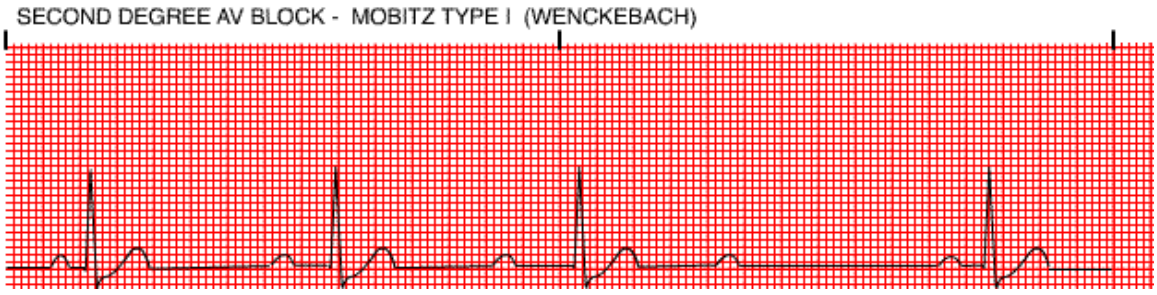


P wave precedes each QRS complex but PR interval is > 0.2 sec

Second Degree A – V block

Mobitz Type 1 block = Wenckebach phenomenon

Conduction from atria to ventricles becomes progressively more difficult, resulting in successive prolongation of the PR interval until a block takes place and the impulse fails to be conducted down to the ventricles. During this pause, the conducting system recovers, and the process starts again.This type of block is located in the AV node.



This is an example of a 4:3 block (4xP waves to 3xQRS complexes)

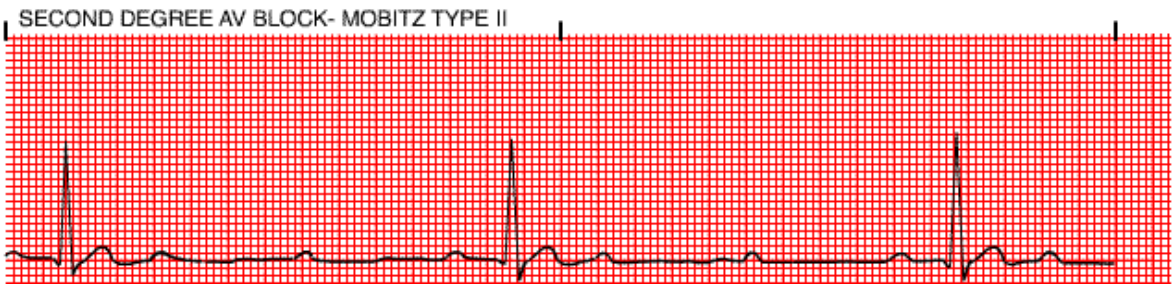
Causes:

1. Inferior myocardial infarction
2. Drugs e.g. digitalis, beta blockers, and occasionally calcium channel blockers.
3. Normal individuals with heightened vagal tone.

Although Mobitz type I block can progress to complete heart block, this is uncommon, except in the setting of acute inferior wall myocardial infarction. Even when it does, however, the heart block is usually well tolerated because the escape pacemaker usually arises in the proximal His bundle and provides a stable rhythm. As a result, the presence of Mobitz type I second-degree AV block rarely mandates aggressive therapy.

Mobitz Type II block

The PR intervals are constant, with some impulses failing to be conducted through the Bundle of His. The site of the block is located lower down than in the Mobitz type I block and when it progresses to complete heart block, the new pacemaker is located further down the conducting system, resulting in a slower, less stable rhythm.
This type of block is *always pathological* and may proceed to complete heart block, making pacemaker implantation necessary in this condition.



This is an example of a 3:1 Mobitz II block (only every third P wave is conducted to the ventricles, so 3x P waves to 1x QRS complex)

Causes:

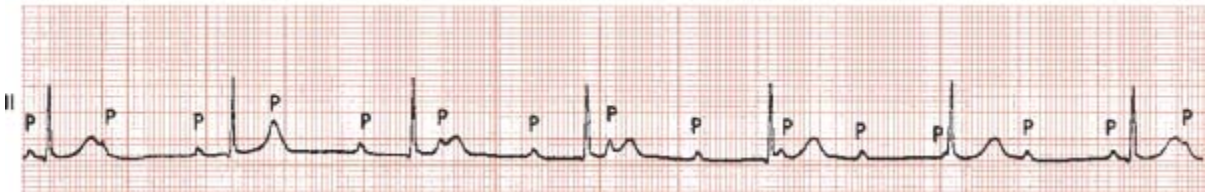
1. Anteroseptal or inferior myocardial infarction
2. Calcific disorders of the fibrous skeleton of the heart.

Third Degree A –V Block

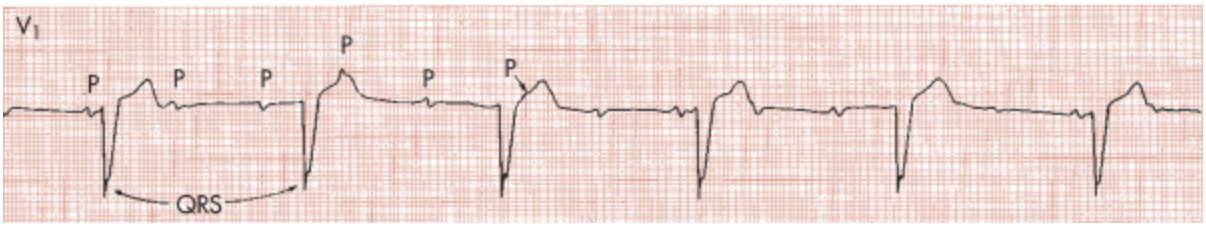
Atrial and ventricular electrical activity occurs independently, with no transmission of impulses from atria to ventricles.

Causes:

1. Lenegre's disease - idiopathic degenerative process involving the conducting system exclusively
2. Lev's disease - calcific process involving valves and conducting system in the elderly
3. Ischaemic heart disease
4. Cardiac surgery → interruption of fibers / oedema
5. Digoxin toxicity
6. Infections e.g. Chaga's disease, tumours
7. Congenital heart disease e.g. ASD, VSD
8. Congenital CHB – an isolated congenital anomaly



Complete heart block with underlying sinus rhythm is characterised by independent atrial (P) and ventricular (QRS complex) activity. The atrial rate is almost always faster than the ventricular rate. The PR intervals are completely variable. Some sinus P waves fall on the T wave, distorting its shape. Others may fall in the QRS complex and be "lost." Notice that the QRS complexes are of normal width, indicating that the ventricles are being paced from the atrioventricular junction (nodal escape rhythm) Compare this example with the following, which shows complete heart block with wide, very slow QRS complexes because the ventricles are being paced from below the atrioventricular junction (ventricular escape rhythm).



This example of complete heart block shows a very slow idioventricular rhythm and a faster independent atrial (sinus) rhythm.

* An idioventricular pacemaker may be located in the His-Purkinje system or the ventricular myocardium.

Bundle Branch Block

Left Bundle Branch Block (LBBB)

Causes:

◦ Hypertensive heart disease (commonest cause)

◦ Coronary heart disease

◦ Left-sided valvular lesion (e.g. calcification of the mitral valve, aortic stenosis, or aortic regurgitation)

◦ Degenerative changes in the conduction system in the elderly.

◦ Cardiomyopathy

Often, >1 contributing factor may be identified (e.g., hypertension and coronary artery disease).
LBBB often correlates with ↓left ventricular function; most patients with LBBB have underlying left ventricular hypertrophy.
Rarely, normal individuals may have a LBBB pattern without evidence of organic heart disease.

Right Bundle Branch Block (RBBB)

Causes:

RBBB may occur in normal hearts or in conditions that affect the *right side of the heart*:

◦ Pulmonary artery hypertension, for example as occurs in COPD

◦ Coronary artery disease.

◦ Right-sided valvular lesions such as pulmonary stenosis

◦ Degenerative changes in the conduction system in the elderly

◦ Atrial septal defect

◦ Pulmonary embolism

◦ Coronary artery bypass graft surgery

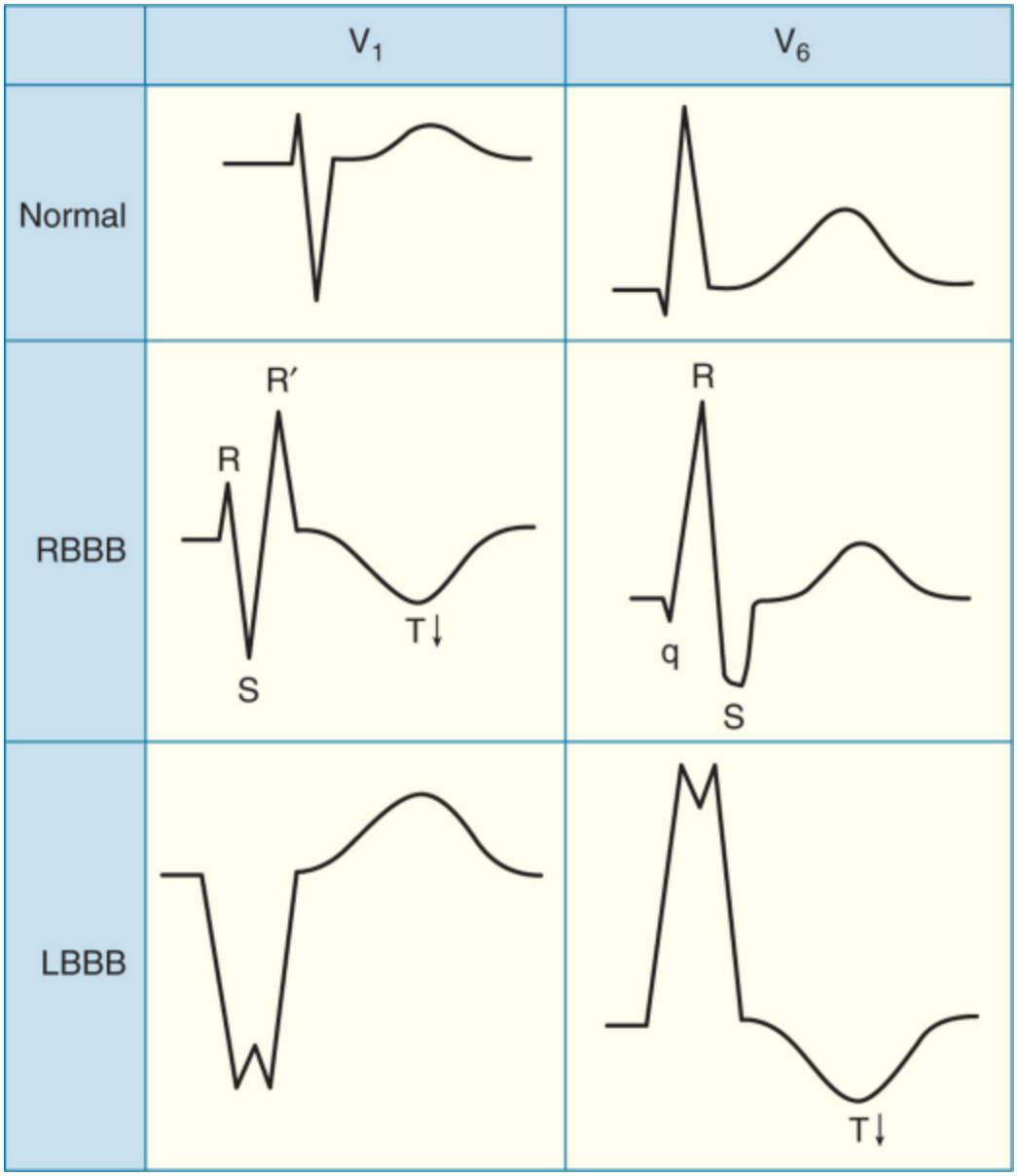
◦ Some normal people have this finding without any underlying heart disorder

In patients with acute anterior wall infarction, a new RBBB may indicate an ↑risk of complete heart block, particularly when the RBBB is associated with left anterior or posterior hemiblock (i.e.a bifascicular block)

Drugs → bundle branch block

- **Anti-arrhythmic** drugs, Class I, such as Na channel blockers
  - · Disopyramide
  - · Procainamide
  - · Quinidine
- **Antidepressants** (tricyclic)
- **Antipsychotic** agents, such as Phenothiazine

Bundle Branch Block



Comparison of typical QRS-T patterns in right bundle branch block (RBBB) and left bundle branch block (LBBB) with the normal pattern in leads V_1 and V_6. Note the secondary T wave inversions (arrows) in leads with an rSR′ complex with RBBB and in leads with a wide R wave with LBBB.

FASCICULAR BLOCKS

The conducting system of the ventricles can be thought of as being made up of three fascicles:

- the right bundle
- the anterior fascicle of the left bundle
- the posterior fascicle of the left bundle

Hemiblocks (unifascicular blocks)

Partial blocks in the left bundle system (left anterior or posterior fascicular blocks) generally do not prolong the QRS duration substantially but instead are associated with shifts in the QRS axis (leftward or rightward, respectively). These are known as hemiblocks (half the left bundle is blocked) or uni-fascicular blocks. Anterior hemiblock is more common than posterior hemiblock, due to the fact that the posterior fascicle has a dual blood supply from both left and right coronary arteries, whereas the left anterior fascicle is supplied solely by the left anterior descending artery.

Bifascicular blocks

Examples of bifascicular block include right bundle branch block and left posterior fascicular block, right bundle branch block with left anterior fascicular block, and complete left bundle branch block.

Chronic bifascicular block in an asymptomatic individual is associated with a relatively low risk of progression to high-degree AV heart block. In contrast, new bifascicular block with acute anterior myocardial infarction carries a much greater risk of complete heart block.

Trifascicular disease

Alternation of right and left bundle branch block is a sign of trifascicular disease. However, the presence of a prolonged PR interval and bifascicular block does not necessarily indicate trifascicular involvement, since this combination may arise with AV node disease and bifascicular block.

Intraventricular conduction delays can also be caused by toxic factors which may lead to hemiblocks, bifascicular blocks or left or right bundle branch blocks, particularly:

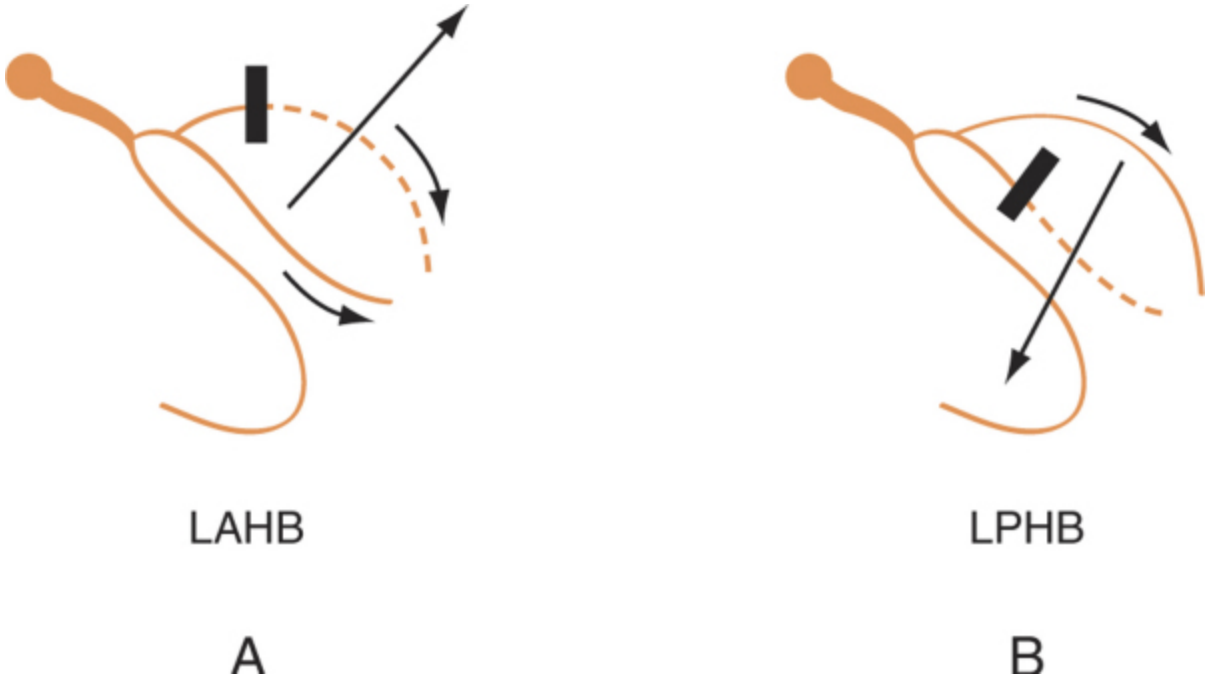
hyperkalaemia

or

drugs, such as:

- Sodium channel blockers
  - Disopyramide (Rhythmodan)
  - Quinidine
  - Procainamide
- Tricyclic antidepressants
- Phenothiazines

Hemiblocks (= half the left bundle is blocked)

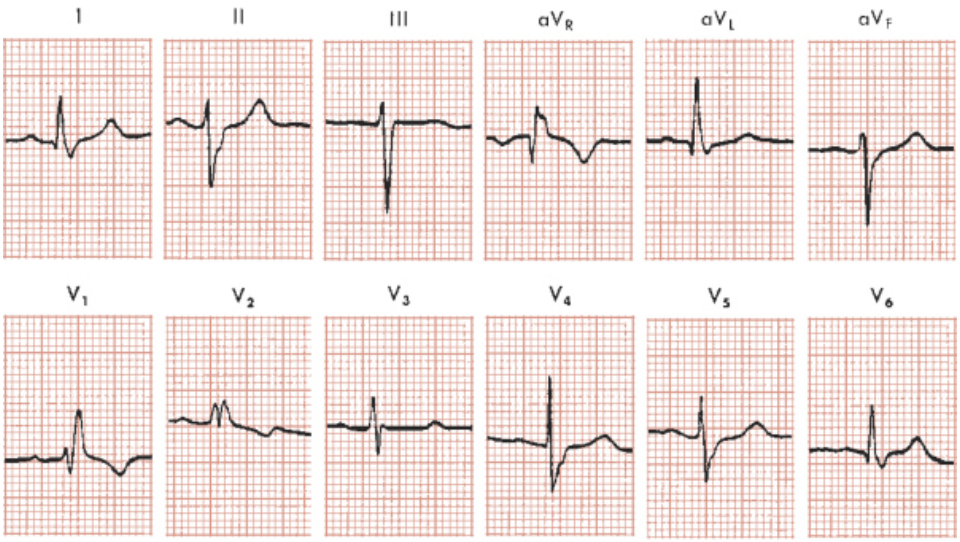


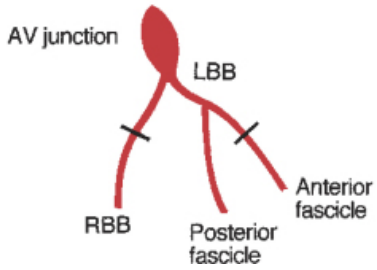
(A) Left axis deviation in left anterior hemiblock (LAHB) aka left anterior fascicular block (LAFB)

(B) Right axis deviation in left posterior hemiblock (LPHB) aka left posterior fascicular block (LPFB)

Bifascicular blocks

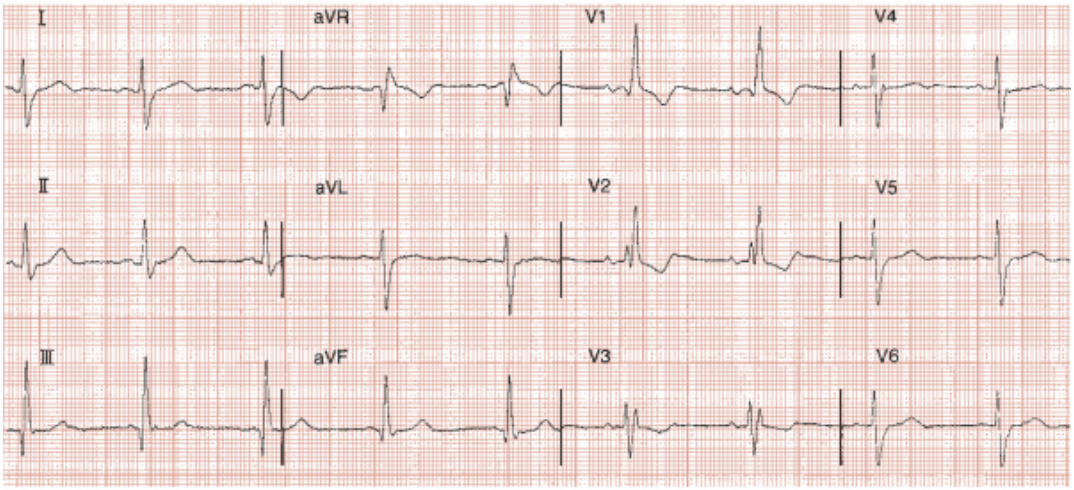
Bifascicular Block: Right Bundle Branch Block with Left Anterior Fascicular Block

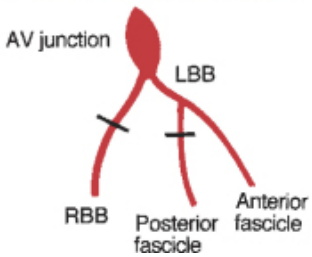




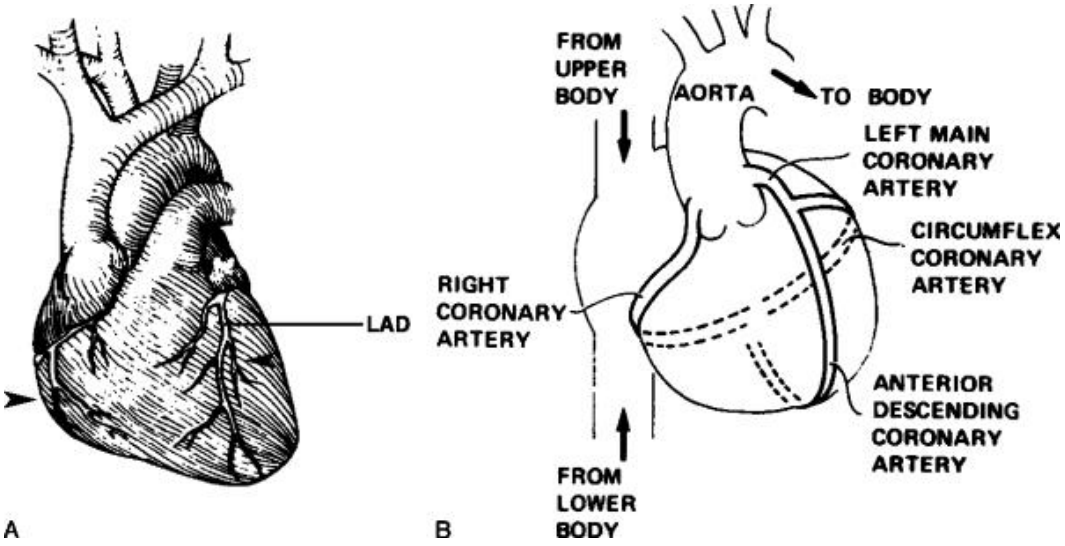
A typical right bundle branch block pattern is present (rSR′ in lead V_1 and qRS in lead V_6). The limb leads show marked left axis deviation, consistent with left anterior hemiblock. Thus a bifascicular block involving the right bundle branch (RBB) and the anterior fascicle of the left bundle branch.

Bifascicular Block: Right Bundle Branch Block with Left Posterior Fascicular Block





A typical right bundle branch block (RBBB) pattern is evident. The limb leads show right axis deviation (RAD). The combination of these two findings (in the absence of other more common causes of RAD such as right ventricular hypertrophy or lateral MI) is consistent with bifascicular block due to left posterior fascicular block in concert with the RBBB. This elderly patient had severe coronary artery disease.



Normal coronary artery anatomy

(A) Anterior view of the heart showing the left anterior descending (LAD) and right coronary arteries

(B) Diagrammatic depiction of the three coronary arteries. The dotted lines represent the atrioventricular (AV) and interventricular grooves *posteriorly*. The continuous parallel lines represent the same grooves *anteriorly*.

Coronary artery areas of supply

Knowledge of the area of myocardium which is perfused by each of the three major coronary arteries is helpful in determining the site of vascular obstruction when an individual has sustained a myocardial infarct.

The **Left Coronary Artery** (LCA) divides into the Left Anterior Descending Artery (LAD) and Circumflex Artery (LCX), which together perfuse the majority of the left ventricular myocardium.

The **LAD** supplies the following areas:

- Anterior wall of LV, apex (V_4), lower part of lateral LV (V_5, V_6) (Diagonal branch)
- Anterior ⅔ ventricular septum ($V_1 – V_4$) (Septal perforator)

The **LCX** generally only supplies:

- Left atrium
- Upper part of the lateral wall of LV (Std I, aVL)
- Posterior LV ($V_7 – V_9$) and inferior LV (Std II, III, aVF) in 15% of individuals

The **Right Coronary Artery** (RCA) supplies:

- Right atrium
- Virtually entire right ventricle (RV) V1, V_3R-V_6R
- Posterior ⅓ ventricular septum
- Postero-inferior LV in 85 % individuals

*The coronary vascular supply of the lateral wall of the LV varies – the diagonal branch of LAD supplies a variable amount of the lower part of the lateral wall; the LCX often supplies the upper part of the lateral wall, but may also supply the lower part. Occasionally, the RCA may extend right around the back of the heart and contribute to the blood supply of the lateral wall of LV.

Blood supply to conducting system:

SA node	RCA 75%, dual 25%
AV node	RCA 80%, left 10%, dual 10%
Bundle of his	LCA 75%, RCA 10%, dual 15%
Left anterior fascicle	LAD
Left posterior fascicle	Dual
Right bundle	LCA

In summary:

LCA supplies:

Most of LV and left atrium
Conducting system below AV node
Contributes to SA and AV nodes

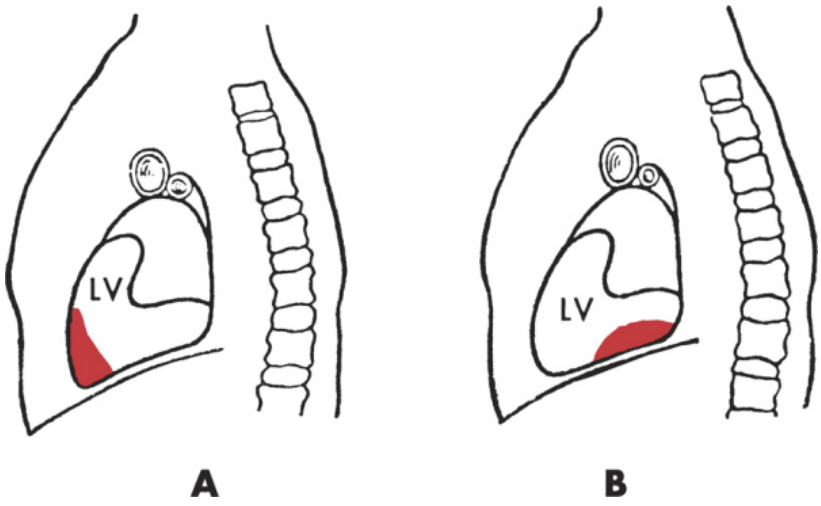
RCA supplies:

Most of RV and right atrium
Inferior and posterior LV (85% of population)
SA and AV nodes
Contributes to conducting system below AV node

Frequency of occlusion of coronary arteries in ischaemic heart disease:

LAD 40 – 50% (antero-septal/extensive anterior MI)
RCA 30 – 40% (inferior MI, often with posterior wall involvement, and in ≤40%, RV)
LCX 15 – 20% (anterolateral MI, with postero-inferior involvement in 15%)

Location of a myocardial infarct



Myocardial infarctions are generally localised to either

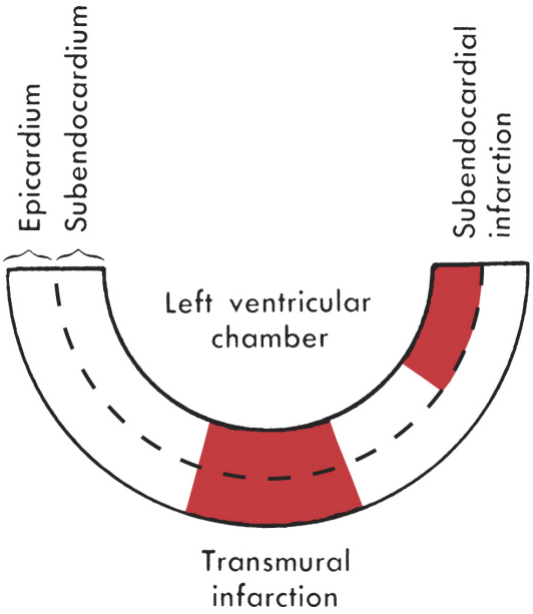
(A) the anterior portion of the left ventricle (LV) or

(B) the inferior (diaphragmatic) or infero-posterior portion of the walls of this chamber.

Unless otherwise specified, the description of a myocardial infarct applies to infarction of an area of **left** ventricular myocardium (right ventricular infarction generally only occurs in conjunction with an inferior MI, caused by proximal occlusion of the RCA).

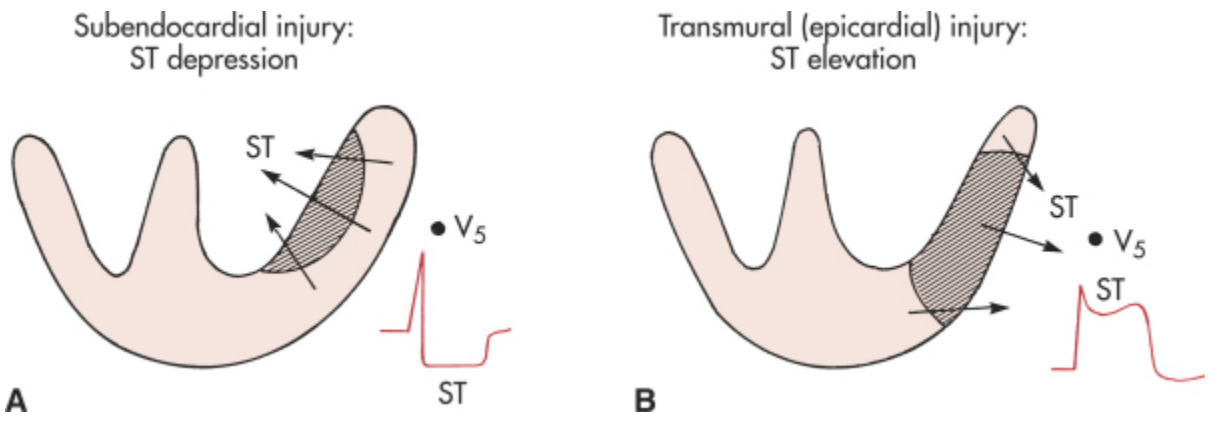
Isolated posterior infarction is uncommon.

Extent of an infarct



Cross section of the left ventricle showing the difference between a *subendocardial* infarct, which involves the inner half of the ventricular wall, and a *transmural* infarct, which involves the full thickness of the wall.

ST segment changes in sub-endocardial and transmural infarction



A With acute subendocardial ischaemia the electrical forces *(arrows)* responsible for the ST segment are deviated toward the inner layer of the heart, causing ST depressions in lead V_5, which faces the outer surface of the heart.

B With acute transmural (epicardial) ischaemia, electrical forces *(arrows)* responsible for the ST segment are deviated toward the outer layer of the heart, causing ST elevations in the overlying lead.

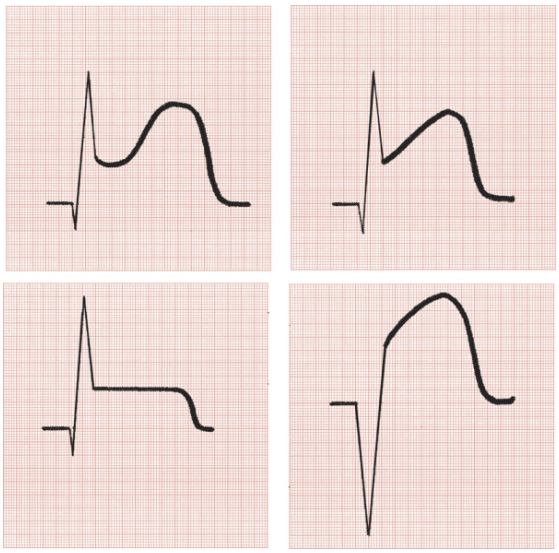
ST elevation myocardial infarction (STEMI)

The earliest ECG changes seen with an acute transmural infarction usually occur in the ST-T complex in two sequential phases.

▫ The *acute* phase is marked by the appearance of ST segment elevations and sometimes tall positive (hyperacute) T waves in the leads which are situated such that they view the area of infarcted myocardium from its epicardial aspect.

▫ The *evolving* phase occurs hours or days later and is characterised by deep T wave inversions in the leads that previously showed ST elevations.

Shape of ST segment in STEMI



The ST segment elevation seen with acute MI may have different shapes, including:

· plateau shaped
· dome shaped
· oblique elevation
· resemblance to a tombstone

Terminology

An *anterior* infarct means that the infarct involves the anterior and/or lateral wall of the left ventricle

The anatomic location of the infarct determines the leads in which the typical ECG patterns appear. For example, with an acute anterior wall MI, the ST segment elevations and tall hyperacute T waves appear in one or more of the anterior leads (chest leads V_1 to V_6 and limb leads I and aV_L).

An *inferior* infarct indicates involvement of the inferior (diaphragmatic) wall of the left ventricle.

With an inferior wall MI the ST segment elevations and tall hyperacute T waves are seen in inferior leads II, III, and aV_F.

Leads showing ECG changes according to the site of infarction

Standard leads II, III, and aVF (↑ST)	inferior
V1, V4R – V6R (↑ST)	right ventricle
V1 – V3 (Prominent R waves and ↓ST)	posterior
V7 – V9 (Q waves and ↑ST)	posterior
V1 – V4 (loss of r waves, ↑ST)	antero-septal
V5 – V6, Std I, aVL	lateral (Std I, aVL upper part lateral wall) (V5 – V6 lower part lateral wall)

ECG indicators of acute ST elevation myocardial infarction (STEMI)

- **Immediate**

  T wave starts to peak, ST segment elevates (ST variable in shape).

- **Within hours**

  Q wave starts developing, ↓height of R wave

Early Q-wave development

- **Day 1 – 2**

  T wave starts to invert, Q wave deepens

Established Q-wave stage

- **Several days later**

  ST starts reverting to normal

- **Weeks – months later**

  T wave reverts to normal (occasionally remains inverted)

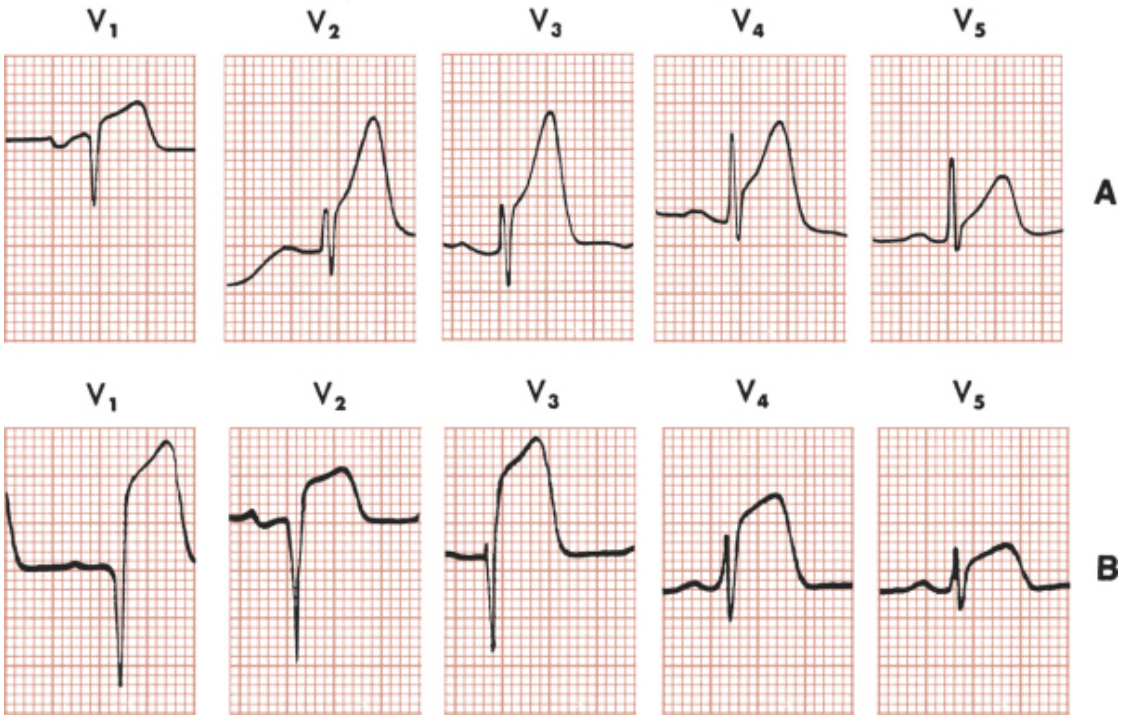
- **Permanent change**

  Q wave usually persists for the lifetime of the patient

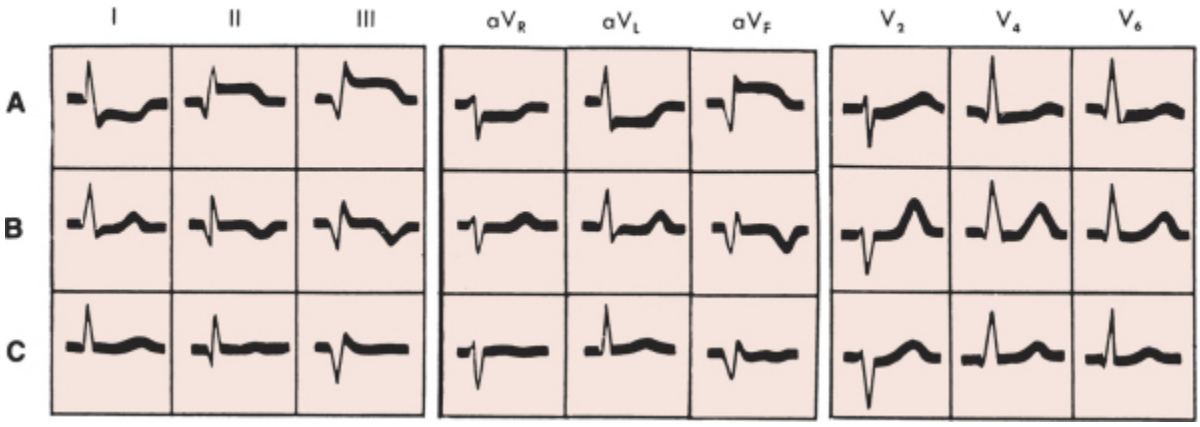
ECG patterns seen in acute myocardial infarction according to the site of the infarct

Acute extensive anterior infarction.

A: In the earliest phase of the infarction, tall positive (hyperacute) T waves are seen in leads V_2 to V_5, with ST elevation in leads $V_1 - V_5$
B: Several hours later, marked ST segment elevation is present in the same leads (current of injury pattern), and abnormal QS waves are seen in leads in V_1 and V_2.



ECG Sequence with Inferior Wall Q Wave Infarction



A, Acute phase of an inferior wall myocardial infarction: ST elevations and new Q waves.

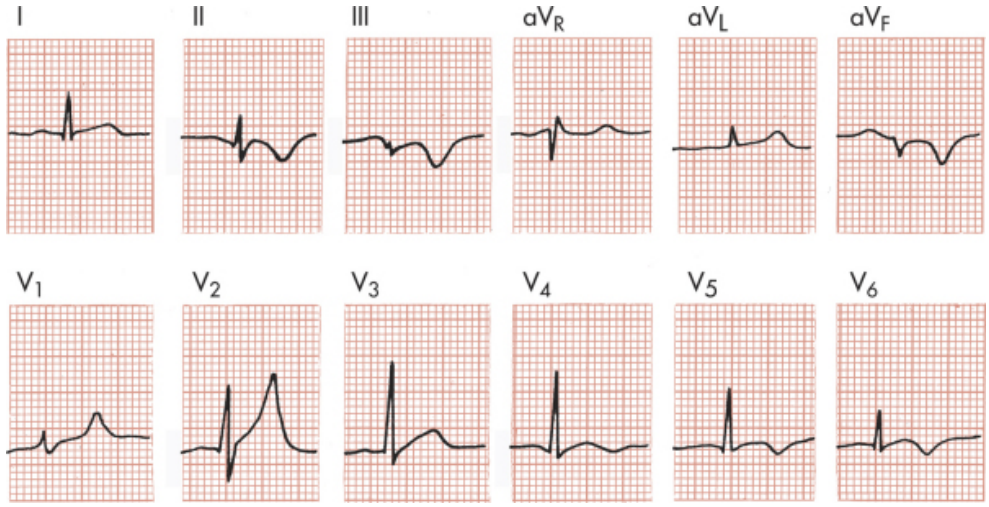
B, Evolving phase: deep T wave inversions.

C, Resolving phase: partial or complete regression of ST-T changes (and sometimes of Q waves).

In **A** and **B,** notice the reciprocal ST-T changes in the anterior leads (I, aV_L, and V_2).

Posterior Myocardial Infarction

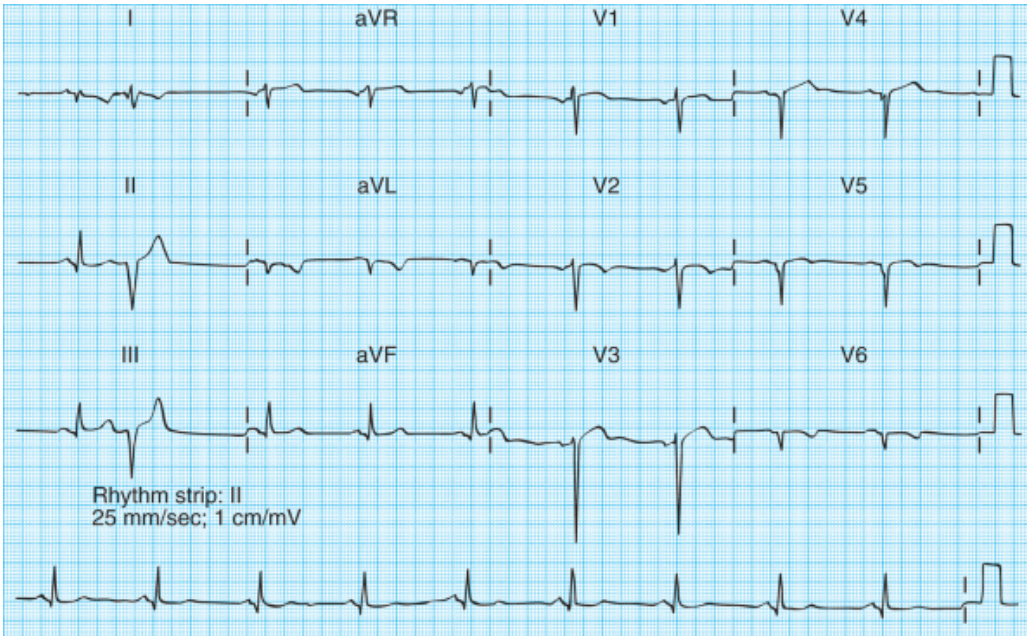
Posterior MI presents a mirror-image pattern of ECG injury in leads V_1 to V_3. The acute phase is characterised by ST segment depression, rather than ST segment elevation. The evolved and chronic phases show increased R wave amplitude and widening instead of Q waves. Other causes of prominent upright anteroseptal forces (tall R waves in V1) include right ventricular (RV) hypertrophy, Wolff-Parkinson-White syndrome, RBBB and HOCM. New appearance of these changes or the association with an acute or evolving inferior or lateral MI usually allows the diagnosis to be made. Extension of the 12 lead ECG to include the posterior leads (V7 – V9) will reveal the classic ECG changes of infarction, as they view the posterior myocardium from its epicardial surface.



Posterior infarction. Notice the tall R waves in leads V_1 and V_2. This patient had a previous inferior infarction (Q waves in leads II, III, aV_F) and probably a lateral infarction as well. Notice reciprocally tall positive T waves in leads V_1 and V_2.

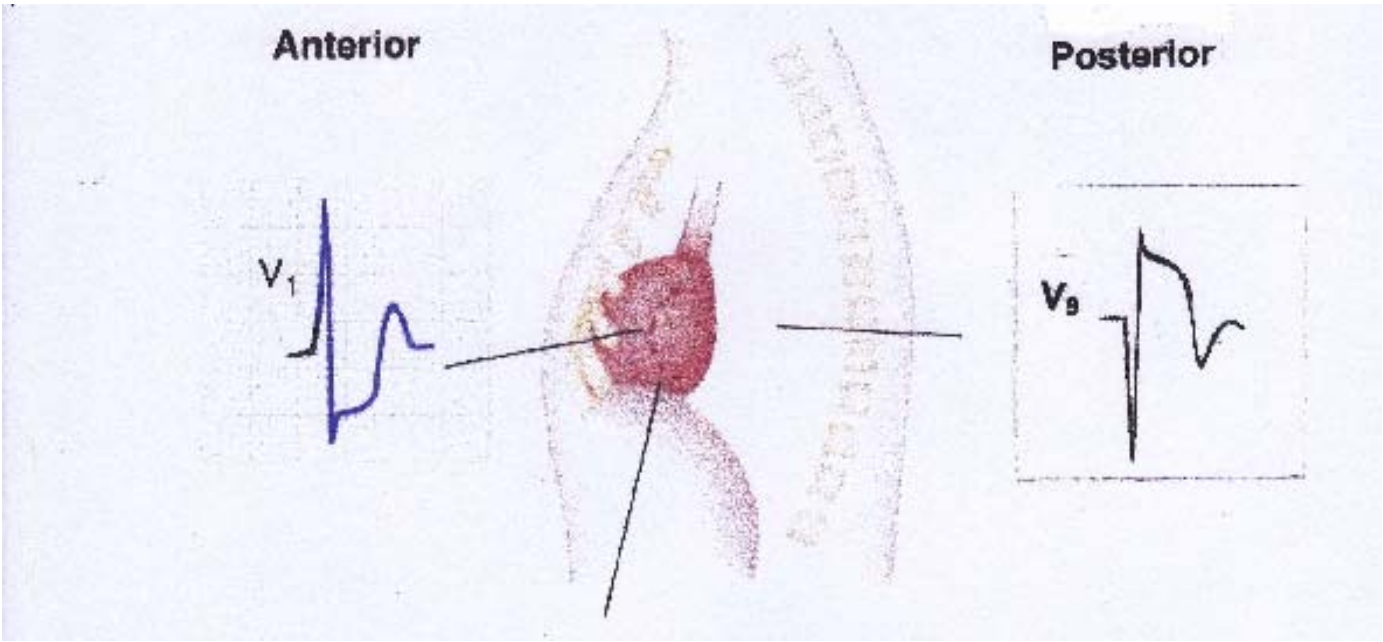
Lateral Myocardial Infarction

Lateral infarction may occur due to occlusion of the left circumflex artery, or to occlusion of the left anterior descending artery or its diagonal branch. It may even occur in association with a right coronary artery occlusion. Extending the ECG to measure posterior leads V_7 to V_9 increases sensitivity for detecting posterior wall injury patterns which may accompany a lateral wall MI.



Example of lateral myocardial infarction. Poor R wave progression in the precordial leads. Deep Q waves in V4 to V_6, Std I and aVL with T wave inversion. Slight ST segment elevation in precordial leads.

Acute Posterior Myocardial Infarction



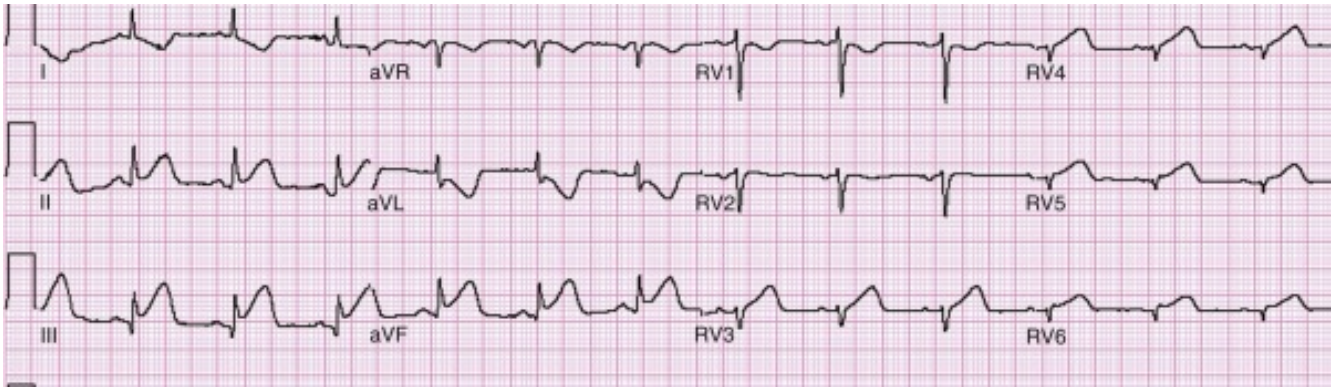
Acute transmural posterior MI

The conventional precordial leads (in particular leads V1 – V3) of the ECG image the posterior wall of the left ventricle from the anterior perspective of the thorax. Acute infarction of the region manifests ECG changes that are frequently the reverse of the typical abnormalities of AMI. In this schematic example, lead V1 reveals ST segment depression with an upright T wave and prominent R wave.

Use of the posterior lead V9, which looks at the epicardial aspect of the posterior wall, (in contrast to lead V1 which looks at the endocardial aspect of the same area) demonstrates the typical changes of acute transmural MI , namely ST elevation and a deep Q wave, these being the mirror image of the changes in lead V1.

Right Ventricular Infarction

Proximal occlusion of the right coronary artery before the acute marginal branch can cause right ventricular as well as inferior acute MI in about 30% of cases. Because the prognosis and treatment of inferior acute MI differ in the presence of RV infarction, it is important to make this diagnosis. The diagnosis is assisted by obtaining right precordial ECG leads, which are routinely indicated for inferior acute MI. Acute ST segment elevation of at least 1 mm (0.1 mV) in one or more of leads V_{4R} to V_{6R} and Q or QS waves effectively identify RV infarction.

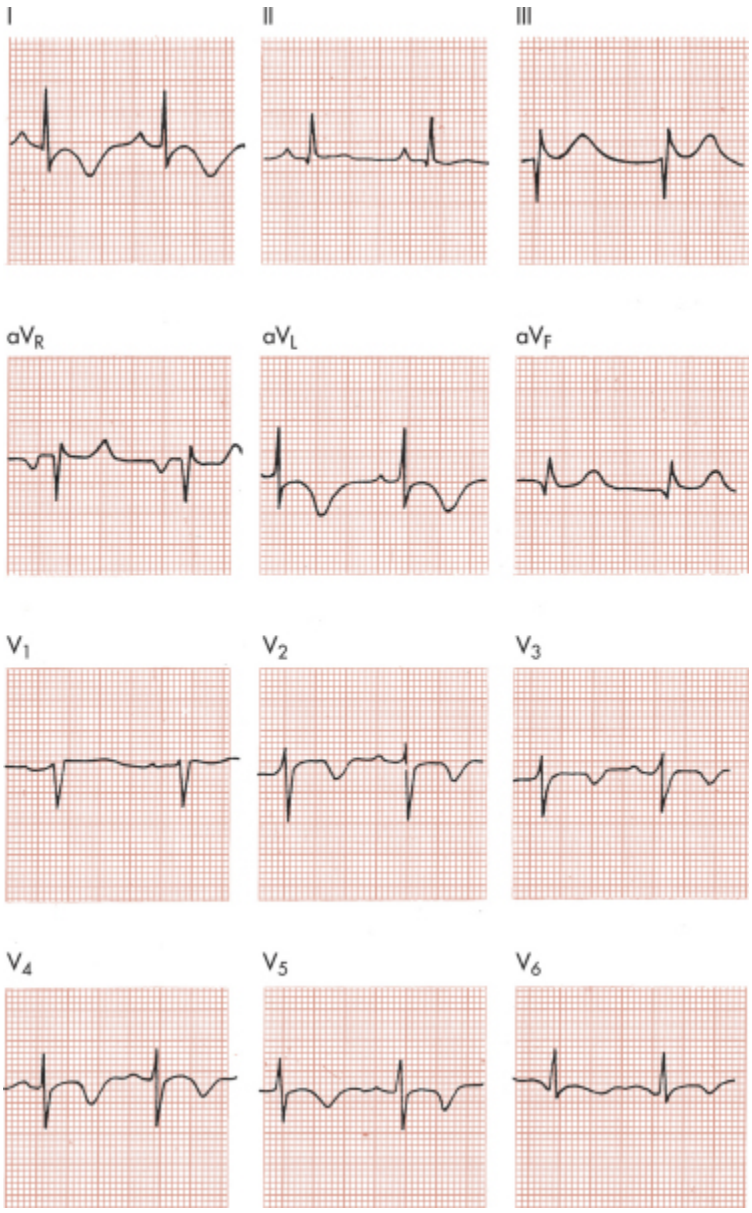


Right ventricular infarction demonstrated with right-sided precordial leads (RV1 to RV6).The ST segment elevation of inferior acute myocardial infarction is present, as is the reciprocal ST segment depression in leads I and aVL. The precordial leads are right-sided chest leads, as might be inferred from the relatively low voltage. ST segment elevation is noted in leads V3R to V6R, consistent with right ventricular infarction.

Non-ST elevation myocardial infarction (non-STEMI)

ECG indicators of non-Q wave MI (non-STEMI, sub-endocardial MI, non-transmural MI)

ST depression rather than elevation, symmetrical T wave inversion, no Q wave, ↑troponin. If extensive, may see reciprocal ST elevation in lead aVR.

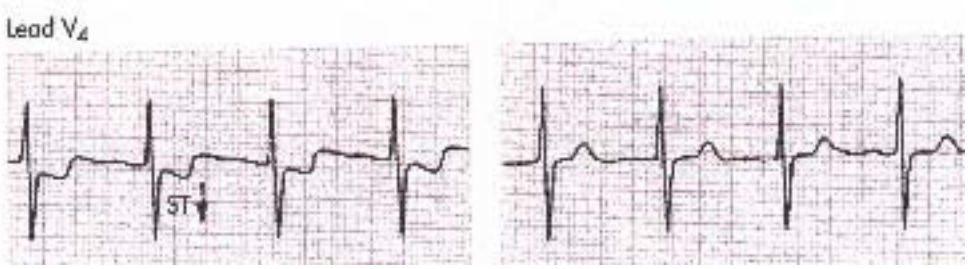


Non–Q wave infarction in a patient who complained of chest pain and also had elevated cardiac enzyme levels.

Notice the deep, symmetrical T wave inversion in leads I, aV_L, and V_2 to V_6. (Prominent Q waves in III and aV_F represent an old inferior wall infarction.)

Angina Pectoris

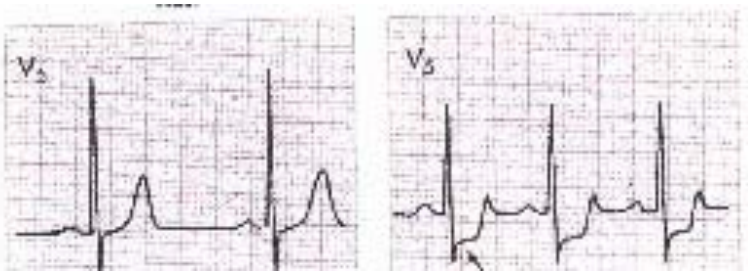
Example 1



A **B**

A. Marked ST depression seen in the ECG from a patient who complained of chest pain while being examined
B. Five minutes later, after the patient was given sublingual nitroglycerin, the ST segments have reverted to normal, with relief of angina.

Example 2



ST segment depression

A **B**

A. Baseline rhythm strip from the positive exercise test of a patient with coronary artery disease.
B. Notice the marked ST depression with increased heart rate.

Biochemical markers used in the diagnosis of acute coronary syndrome

1. Troponin I or Troponin T
2. CK-MB
3. C-reactive protein (CRP)
4. Brain natriuretic peptide (BNP)

Troponins

Troponin is a complex of three protein sub-units, which are attached to the tropomyosin strand in cardiac muscle.

Troponin C (calcium binding) not cardiac specific, also found in skeletal muscle
Troponin T (tropomyosin-binding) also not cardiac muscle specific – rises in MI as well as in renal failure, pneumonia, PE, liver disease, stroke, carcinomas, CCF.
Troponin I (inhibitory) is sensitive and specific to myocardium.

Troponin level starts to rise 4 – 6 hours after myocardial injury, peak levels attained at 12 – 48 hours and remains elevated for up to 2 weeks.
Either Troponin T (TpT) or Troponin I (TpI) may be used as a marker
↑Troponin is a marker for myocardial damage and is a strong predictor for recurrent ischaemic events

CK-MB

Troponin is more sensitive to myocardial damage than is CK-MB, therefore its use has led to ↑diagnosis of MI, compared to when only CK-MB was used as the marker, as those patients with a small area of myocardial necrosis would have had no CK-MB elevation and so would have been labelled as unstable angina.
CK may be measured as a total or as the MB fraction. This marker is useful to assist in diagnosis of a recurrent infarct in the acute setting, when the troponin level may still be elevated from the initial MI. The CK remains elevated for only ± 48 hours.

C-reactive protein (CRP)

CRP is a marker for inflammation of the vessel wall involved in the occlusion. It has been found to have the ability to actually increase the size of the infarcted area.
CRP is an independent marker of adverse outcome in the acute coronary syndrome.

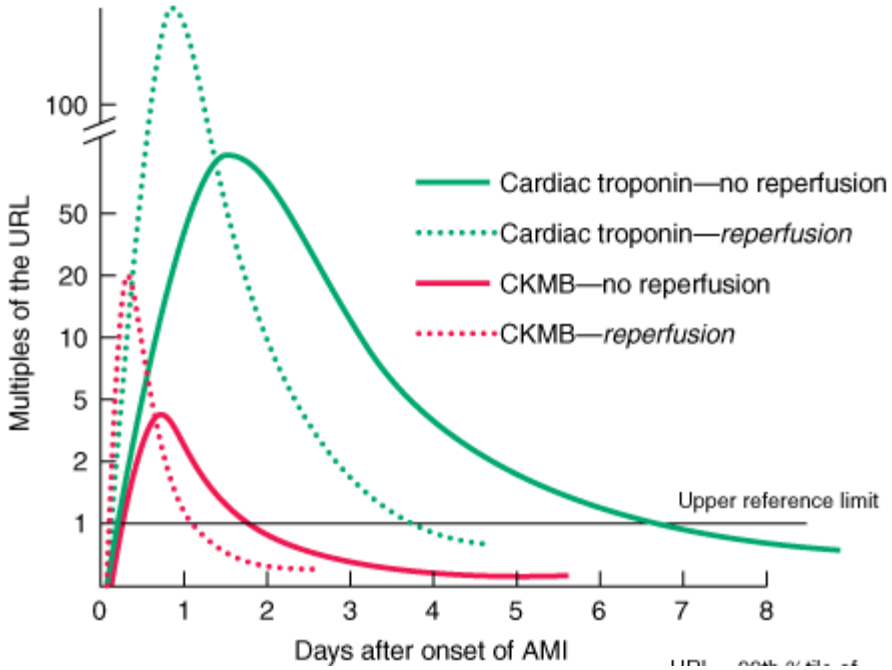
Brain natriuretic peptide (BNP)

BNP was so-called because it was first identified in porcine brain, but now known to be formed predominantly in ventricular muscle. Its level increases rapidly in the first 24 hours post MI, peaking at 12 – 20 hours. There may be a second peak 2-5 days later in an extensive MI.
BNP is a predictor of heart failure and ↑mortality. Patients with ↑levels have double the risk of death over the subsequent 2 years post MI, compared with patients with no elevation in BNP.

The level of BNP can rise even in unstable angina without myocardial necrosis, and is also a predictor in these patients of heart failure and death.

Diagnostic criteria for acute MI

↑Troponin or ↑CK-MB
and
Symptoms of myocardial ischaemia ***or*** **ECG changes of MI**



Typical cardiac biomarkers that are used to evaluate patients with STEMI include the MB isoenzyme of CK (CKMB) and cardiac-specific troponins. (URL=upper reference limit)

Ischaemic Heart Disease - facts and figures

Pathology

≤ 50% occlusion of a coronary artery results in angina on effort
50% – 80% occlusion causes angina at rest
> 80% occlusion will result in myocardial infarction

History

Silent myocardial ischaemia (ischaemia which is asymptomatic or not recognised by the individual as an illness) occurs in 70% of cases of angina and 20% of cases of myocardial infarction. These figures are higher in diabetics and in the elderly.

ECG

- In the early stages of a myocardial infarction, > 50% of patients show no diagnostic changes on ECG. Ultimately, most of these patients develop characteristic ECG changes, but 10% fail to show any ST changes.
- The majority of MIs appear to be non-STEMIs; 70% of enzyme proven MIs show no ST elevation or Q waves on ECG.

- Of the patients who demise as result of their myocardial infarct, 60% do so before they reach hospital, the cause most often being ventricular fibrillation.

Poor prognostic features post MI

Clinical Features	ECG features	Markers
Increased age	Anterior location	↑↑BNP
Low systolic BP	Hyperacute T waves	↑↑CRP
Tachycardia	Marked ST elevation	
Pulmonary oedema		

Acute Pericarditis

Aetiology

Although there are many causes of acute pericarditis, in most cases the cause is unknown (idiopathic) or due to viral infection.

Clinical Manifestations

- **Chest pain**

Chest pain of acute infectious (viral) pericarditis typically develops in young adults (18 to 30 years) 1 to 2 weeks after a viral illness

The symptoms are sudden and severe with retrosternal or left precordial pain and referral to the back and trapezius muscle area.

Radiation to the arms may occur. The pain is often pleuritic in nature and may be aggravated (supine or left lateral decubitus posture) or relieved (upright posture) by changes in posture.

- **Fever**

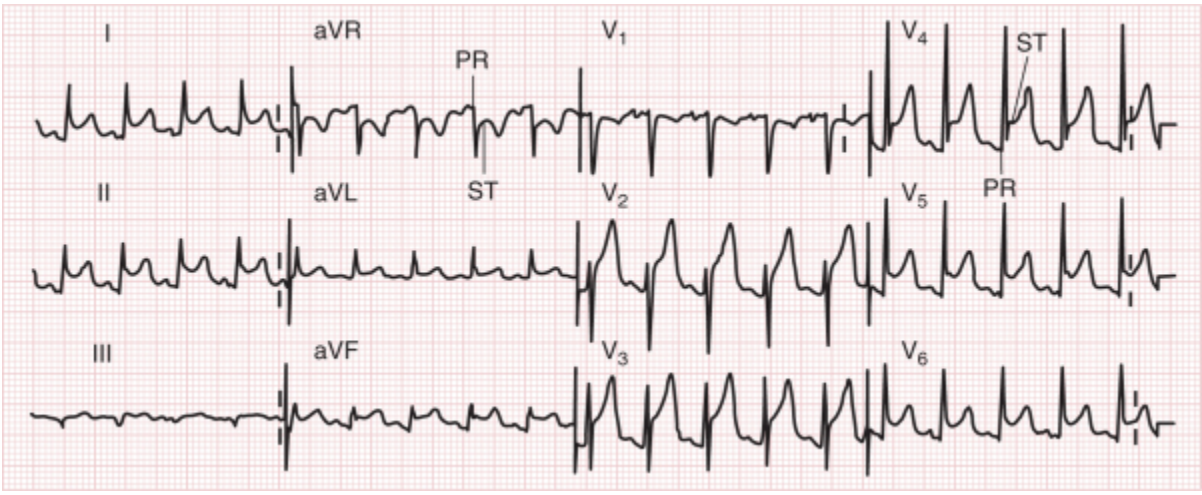
Pain may be preceded by low-grade fever.

Physical examination

- Pericardial friction rub often best heard in the supine or left lateral decubitus posture.
- Low-grade fever,
- Sinus tachycardia
- Atrial ectopy
- Atrial fibrillation (unusual)

Diagnosis

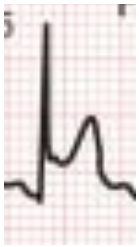
- **Electrocardiographic changes** are common, consisting of ST segment elevation and PR segment depression reflecting atrial involvement. After several days, the ST segments normalise and then the T waves become inverted. Q wave development does not occur. A pericardial effusion may occur and then tachycardia, loss of R wave voltage, and electrical alternans also may be seen



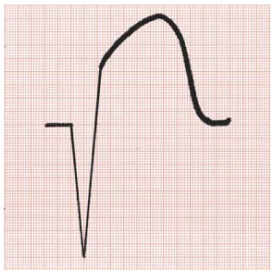
Acute pericarditis Note the diffuse ST-T wave changes and PR elevation in lead aVR and PR segment depression in leads II and aVF and in the precordial leads.

The ST segments in acute pericarditis are typically concave in appearance (so-called "saddle-shaped") in contrast to the coved appearance of the ST segments in acute MI. However, they may appear very similar in configuration.

Up to 25% of patients with a transmural MI develop acute pericarditis 2 – 3 days post infarction.



ST segment elevation in acute pericarditis; note PR segment depression & absence of pathological Q wave



Coved ST segment in acute ST elevation MI; note deep QS wave, isoelectric PR segment.

• **Blood tests** reflect an inflammatory state, with:

·↑ ESR

·↑ C-reactive protein level

·↑ White cell count.

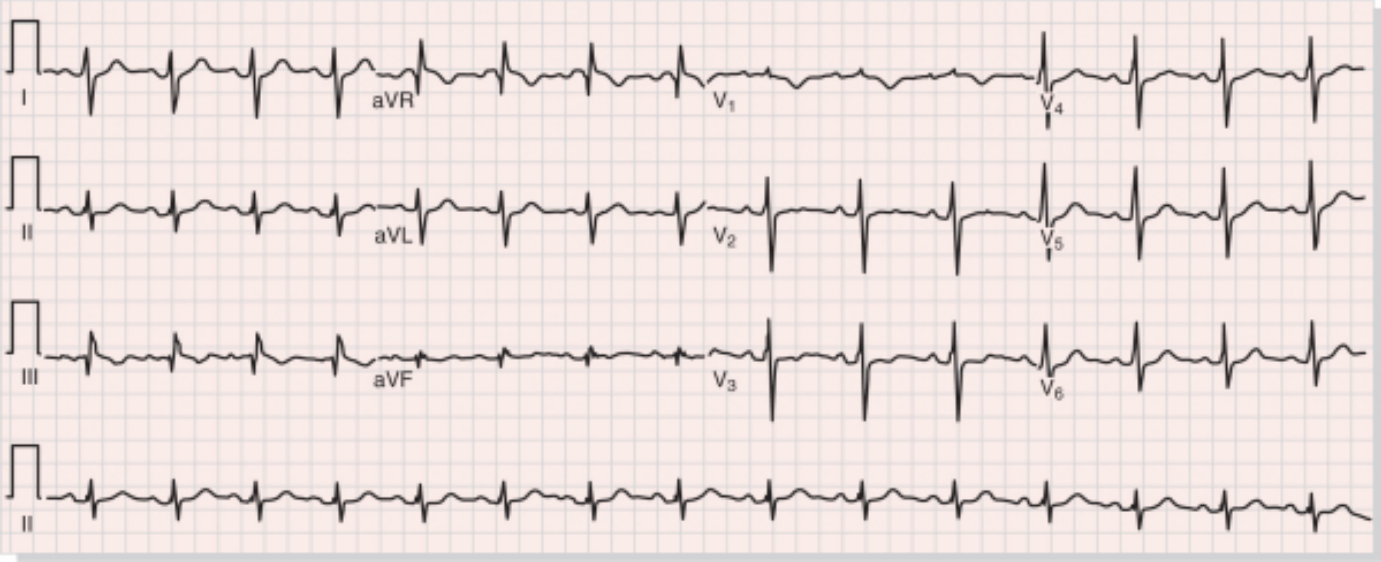
·Mildly ↑ creatine kinase MB fraction and ↑troponin level in up to half of patients and are thought to represent epicardial inflammation rather than myocardial necrosis.

Acute Pulmonary Embolism

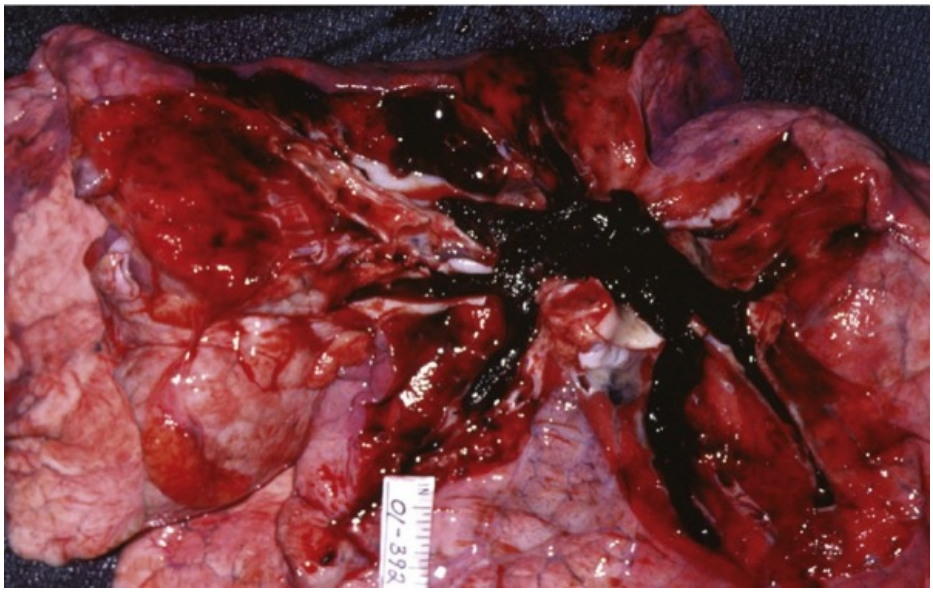
ECG

- Sinus Tachycardia (one of the most common ECG findings in this situation)
- T wave inversion V1–V4 due to right ventricular strain (commonest ECG abnormality in PE)
- Ventricular ectopic beats
- Atrial fibrillation
- Right bundle branch block
- SIQ3T3

S1 (Deep S wave in Standard Lead I) signifies development of acute right axis deviation due to sudden increase in right sided pressure and right ventricular dilatation.Deep Q waves and T wave inversion develop in Standard Lead III - ? rationale for this



Electrocardiogram (ECG) showing SIQ3T3



Massive pulmonary embolism on autopsy. This man died with a large clot burden that plugged the distal lobar arterial branches, eventually producing nearly complete obstruction to blood flow and subsequent cardiac arrest. This man had vague respiratory symptoms for 2 weeks, causing him to see a physician who diagnosed bronchitis.

Sudden cardiac death

Definition

Sudden cardiac death is an instant unexpected death which occurs within one hour of an abrupt change in a person's stable clinical state. The mechanism is generally a ventricular tachyarrhythmia.

The underlying pathology is usually coronary heart disease in middle-aged and elderly persons. Especially at risk are individuals who have a residual myocardial scar post MI, particularly if the left ventricular ejection fraction is severely reduced (to approximately 30%). These patients ideally should have an implantable cardiac defibrillator inserted.

In children and young athletes the two main causes of sudden death are long QT syndrome and hypertrophic cardiomyopathy.

Loss of consciousness and family history of sudden cardiac death should encourage the physician to examine the patient's relatives.

Congenital Long QT Syndrome

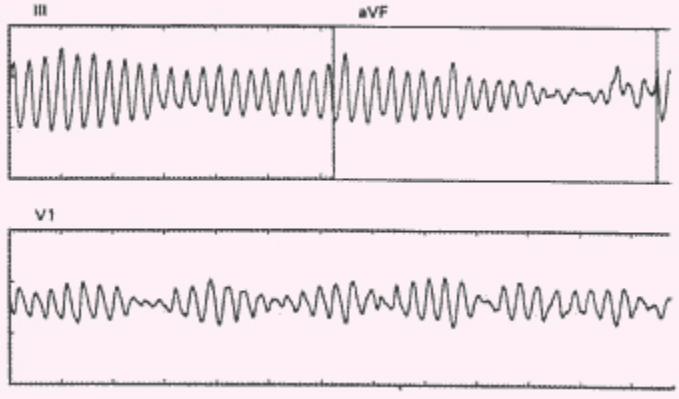
Clinical Presentation

There are severe and mild forms. In the severe forms, the affected subjects usually experience syncope due to ventricular arrhythmias during the first decade of life and sometimes in early childhood.

These ventricular tachycardias are most often induced by physical exercise or by emotion, but can also occur at rest. Cardiac arrest can be the first presentation of the disease.

Mild forms can be revealed when the individual, who is an asymptomatic carrier of a genetic defect, ingests a medication that affects ventricular repolarisation and triggers torsades de pointes and syncope.

Rhythm strips showing torsade de pointes



There is alternating electrical polarity and periodic twisting of the points of the QRS complex around the isoelectric line.

Genetic Origin of the disease

The long QT syndrome (LQTS) is inherited as an autosomal dominant condition. Asymptomatic carriers are numerous, probably around 5 to 10 per 100,000 persons (0.01%).

Management

Avoidance of competitive sports.
Parents and siblings of diagnosed individual with LQTS should be examined by a cardiologist.
A list of the contra-indicated drugs should be given to each affected member of the family.
Treatment by beta-blockers at maximum tolerated dose prevents most of the cases of syncope and sudden death.
Implantation of a pacemaker (in patients who are symptomatic from beta-blocker induced bradycardia) or implantable defibrillator may be required in high risk cases.

Other Causes of long QT interval

- Drugs e.g. amiodarone, exacerbated by grapefruit
- Cardiac pathology (ischaemia/MI, myocarditis, CCF)
- CNS events (head injury, sub-arachnoid haemorrhage, syncopal attack)
- Hypocalcaemia, hypokalaemia, hypomagnesaemia
- Hypothermia
- Hypothyroidism

Hypertrophic Cardiomyopathy (HOCM)

Clinical Presentation

Sudden cardiac death constitutes the most devastating aspect of obstructive and non-obstructive hypertrophic cardiomyopathy. The diagnosis of hypertrophic cardiomyopathy is usually based on ECG and echocardiography. Loss of consciousness associated with ventricular tachycardia identifies patients at very high risk of sudden cardiac death. Of the causes of sudden death in athletes, HOCM is the cause in approximately 25% of cases.

Genetic Origin of the disease

It is inherited as an autosomal dominant. The prevalence of the disease is 0.2%. Penetrance of the genetic abnormality is variable, and genetic studies have shown that approximately 20% of genetically affected adults are healthy carriers without any ECG or echocardiographic abnormality.

Treatment

Drug treatment: Beta blockers, Verapamil, Amiodarone

Surgery: myomectomy – surgical removal of part of the hypertrophied myocardium

Alcohol injection into the septum to sclerose the area

Implantable cardiovertor/defibrillator

ECG features of HOCM (93% of patients with HOCM have ECG abnormalities)

- Left atrial abnormality, due to ↓ventricular compliance and coexistent mitral regurgitation.
- LVH (tall R waves and LV strain pattern in lateral chest leads)
- Prominent septal Q waves in the lateral leads (Std I, aVL, V5, V6)
- Tall, broad R waves in V1
- AV conduction defects may occur

Effect of electrolyte disturbances on the ECG

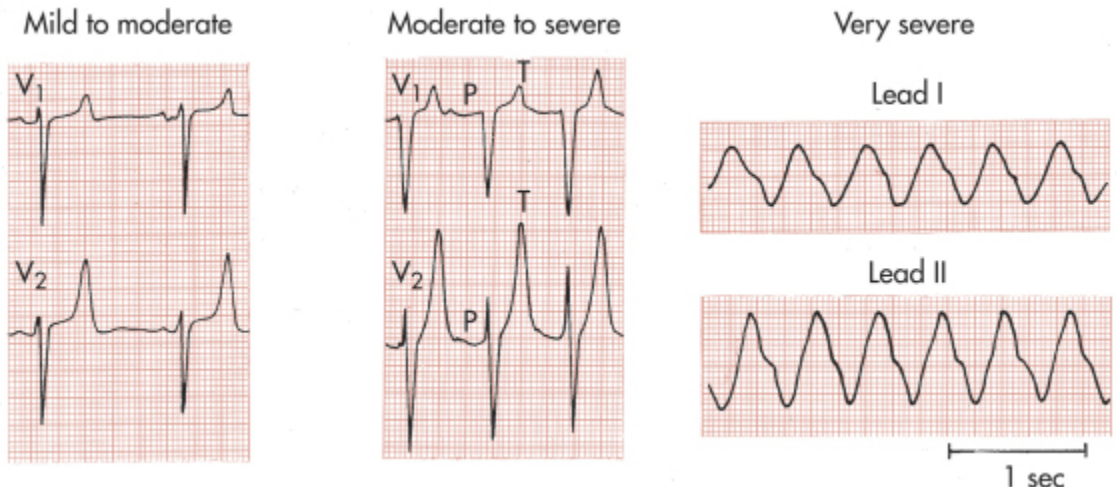
Potassium

Hyperkalaemia (Serum Potassium level > 4.5 mmol/L)

Rhythm	Sinus bradycardia; nodal/ventricular arrhythmias
P wave	flattens, may disappear
PR interval	prolonged
QRS	widens
ST segment	shortens and elevates
T waves	tall, peaked
QT interval	short (due to short ST segment)

Finally, the ECG pattern becomes that of a sine wave, and ventricular fibrillation or asystole occur unless the K+ level is reduced timeously.

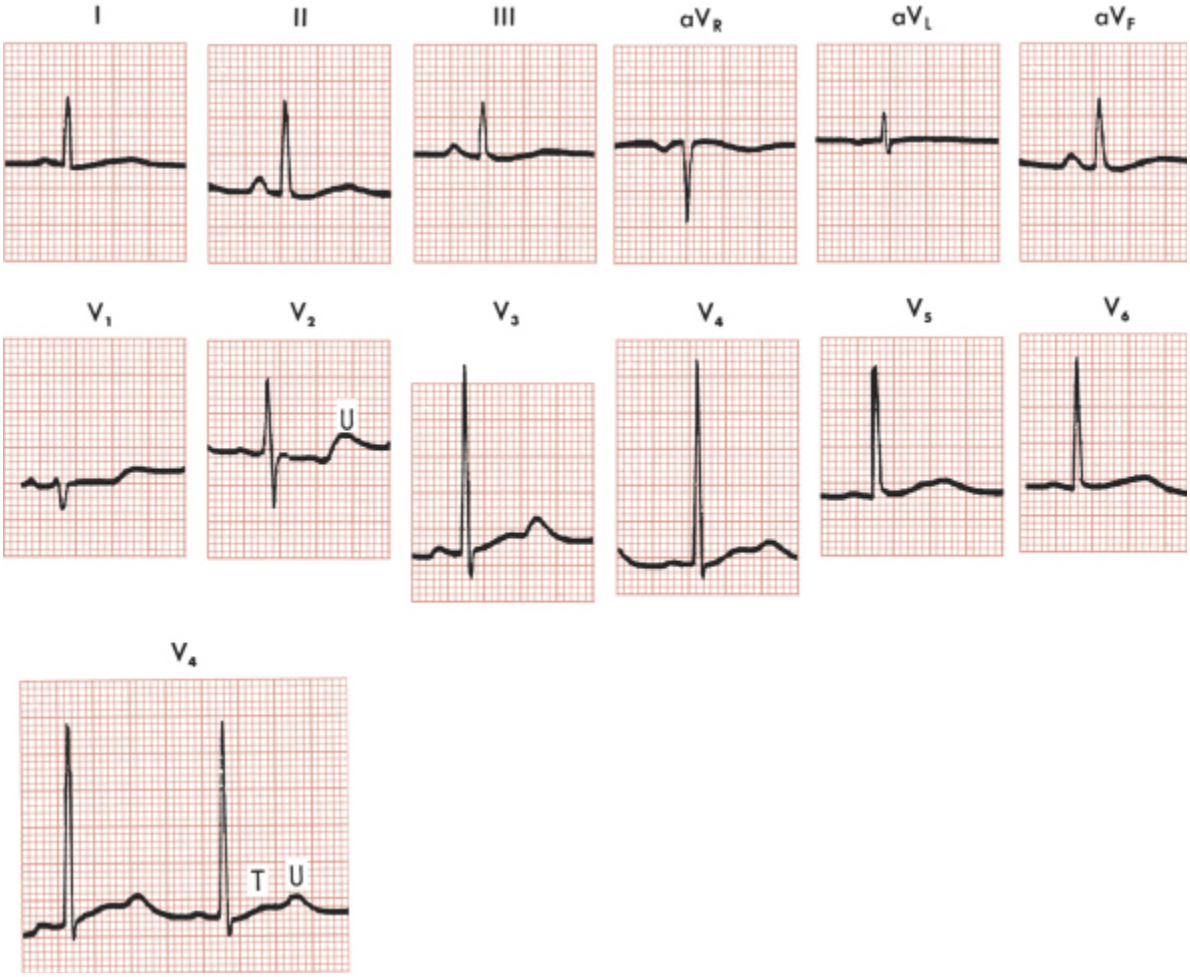
In short, P wave flattens and PR interval lengthens; T wave peaks and QT shortens
QRS progressively widens and arrhythmias and AV blocks may occur.



The earliest change with hyperkalaemia is peaking ("tenting") of the T waves. With progressive increases in the serum potassium concentration, the QRS complexes widen, the P waves decrease in amplitude and may disappear, and finally a sine-wave pattern leads to asystole or ventricular fibrillation.

Hypokalaemia (Serum Potassium level < 3.2 mmol/L)

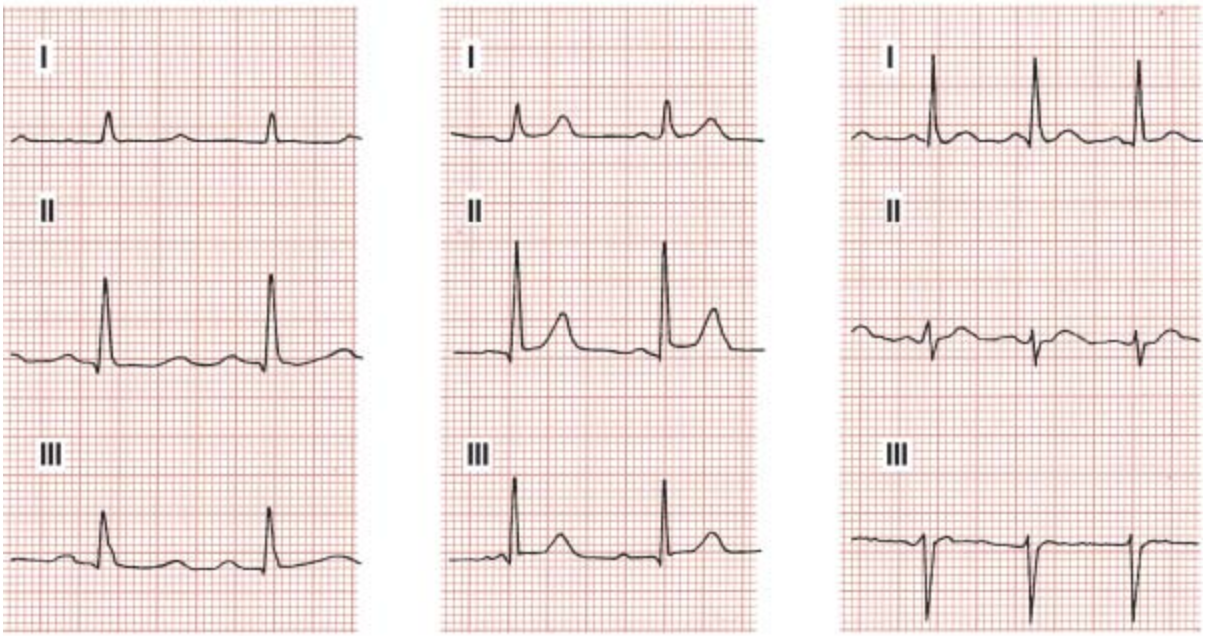
Rhythm	atrial/ventricular arrhythmias
P wave	prominent
PR interval	prolonged
ST segment	depressed
T waves	flattened, may invert
U waves	prominent
QT interval	normal, but cannot always be accurately measured, because the T waves and U waves often merge



ECG leads from a patient with a markedly low serum potassium concentration of 2.2mmol/L. Notice the prominent U waves, with flattened T waves.

Calcium

Hypocalcaemia **Normal** **Hypercalcaemia**



Hypocalcaemia prolongs the QT interval by stretching out the ST segment. Hypercalcaemia decreases the QT interval by shortening the ST segment so that the T wave seems to take off directly from the end of the QRS complex.

High serum calcium concentrations may lead to coma and death. A short QT interval in a patient with mental status changes is sometimes the first clue to the diagnosis of hypercalcaemia.
Patients may, however, have clinically significant hypocalcaemia or hypercalcaemia without diagnostic ECG changes.

DIGOXIN

Digoxin is a cardiac glycoside

Mechanism of Action

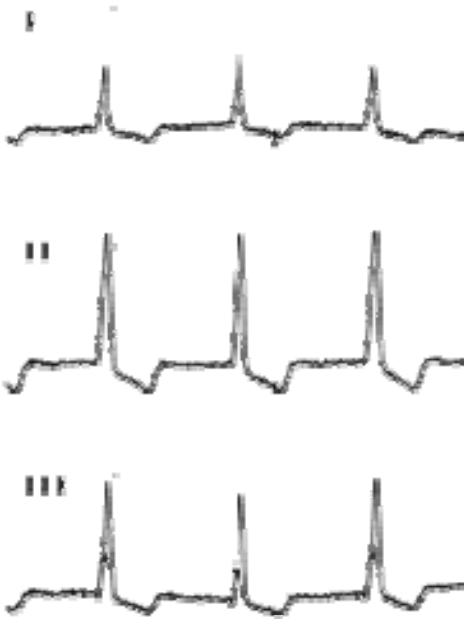
- Slows heart rate
  In sinus rhythm, slows rate of discharge of SA node. → sinus bradycardia
  (−ve chronotropic effect)

- Slows AV conduction
  The reason for the use of digoxin in atrial fibrillation is that it slows AV conduction by increasing vagal activity via an action on the CNS; this → slowing of the ventricular rate. Even though the atrial dysrhythmia is still present, the slowing of the conduction allows for increased efficiency of the heart due to increased ventricular filling time.

- ↑Force of Contraction
  Digoxin inhibits the Na+/K+ pump. The increased Na+ concentration inside the cardiac myocyte slows extrusion of Ca++ via the Na+/Ca++ exchange transporter
  Increased Ca++ stored in the sarcoplasmic reticulum increases the amount of Ca++ released in each action potential → more powerful contraction
  (+ve inotropic effect)

Clinical use of Digoxin

- To slow rate in AF
- Treatment of heart failure in patients who remain symptomatic despite optimal use of diuretics and ACE-inhibitors



The inverted tick appearance of the ST segment and T wave which occurs in individuals who are on treatment with digoxin. Other characteristic ECG features are a prolonged PR interval and a short QT interval.

Digoxin Toxicity

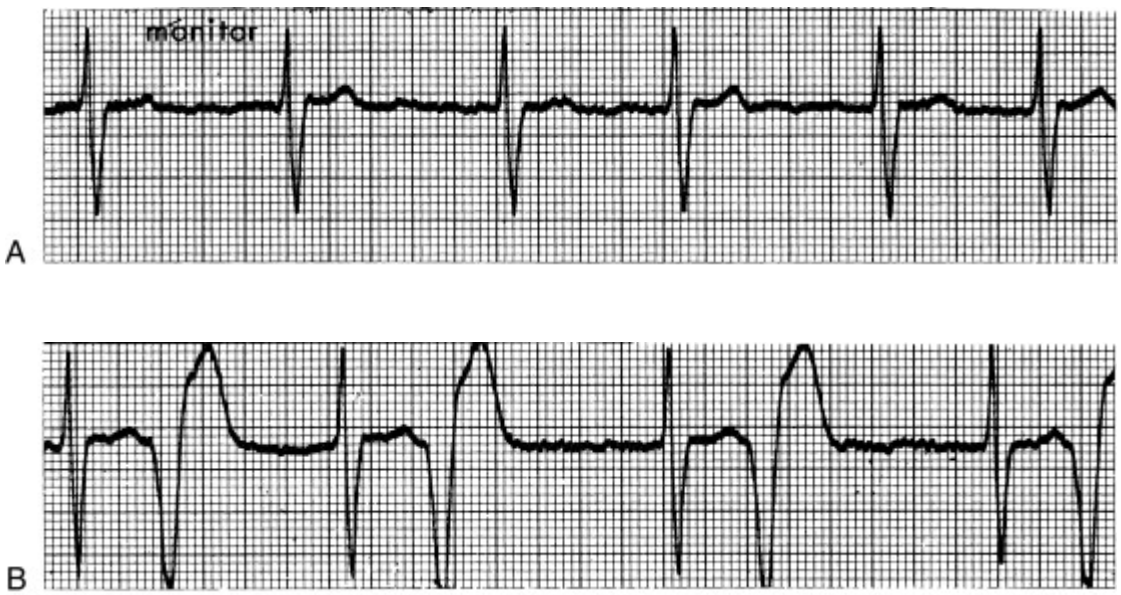
Fatigue, malaise and weakness are common.

Cardiac, gastrointestinal and central nervous systems are affected. Electrolyte disturbances may be present.

CARDIAC: Most common and often first finding is an increase in premature ventricular complexes. Almost any dysrhythmia can occur but *simultaneous increased automaticity of cardiac tissue and conduction delay in the AV node should raise suspicion*. Findings suggestive of toxicity include:

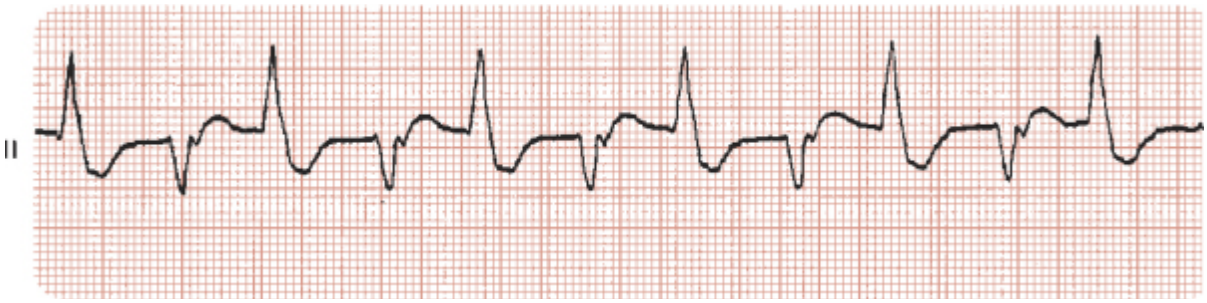
- Frequent premature ventricular complexes, ventricular bi- and trigeminy
- Bradyarrhythmias
- AV block (Mobitz type 1)
- Atrial tachycardia with AV block
- Junctional tachycardia
- Bidirectional ventricular tachycardia

Ventricular bigeminy caused by digoxin toxicity



Ventricular ectopy is one of the most common signs of digoxin toxicity. The underlying rhythm in **A** is atrial fibrillation. In **B** each normal QRS is followed by a ventricular premature beat.

Bidirectional Ventricular Tachycardia



This digitalis-toxic arrhythmia is a special type of ventricular tachycardia with QRS complexes that alternate in direction from beat to beat. No P waves are present.

GI: Anorexia, nausea, vomiting, diarrhoea, abdominal pain.

CNS: Headache, dizziness, visual disturbance (flashing lights, halos, blurred vision, change in colour perception, decreased visual acuity), confusion, hallucinations, delirium.

Electrolyte disturbance: Hyperkalaemia is often seen in acute poisoning, due to inhibition of the Na+:K+ pump (K+ stays in ECF)

Hypokalaemia is more common in chronic toxicity

Treatment of Toxicity

- Acute toxicity: activated charcoal if within 1 hr of ingestion.
- Treat electrolyte disturbances: hyperkalaemia (with for example glucose and insulin) hypokalaemia and hypomagnesaemia.
- Digoxin-specific Fab fragments (Digibind)
- Bradycardia and heart block: Atropine, temporary pacemaker if symptomatic
- Ventricular tachycardia: Lidocaine or phenytoin, which decrease ventricular automaticity without slowing AV node conduction.

A high index of suspicion helpful. To minimise toxicity, digoxin levels should be checked particularly if there is a change in the patient's condition (e.g., weight loss, worsening renal function) or an interacting drug is started or stopped.

Haematology – learning objectives

Essential

Pre reading

- ✓ *Understand the components of a FBC: red cells (Hb, MCV, PCV/Haematocrit, reticulocytes), platelets; white cells (total count and differential – lymphocytes + granulocytes (monocytes, neutrophils, eosinophils, basophils)* reading pp
- ✓ *Normal development of white and red cells (marrow production of immature forms, maturation in marrow to mature forms, which are then released into circulation etc)*
- ✓ *Coagulation pathways (extrinsic and intrinsic)*

In course

- ✓ Understand the common causes of polycythaemia (primary + secondary: smoking)
- ✓ Understand the 5 common anaemias:
- ➢ Iron deficiency using chronic blood loss as an example
- ➢ Megaloblastic anaemia using the examples of pernicious anaemia and dietary folate deficiency
- ➢ Chronic disease using the example of rheumatoid arthritis
- ➢ Haemolytic anaemia using sickle cell disease as a clinical example
- ➢ Acute blood loss using post-operative haemorrhage as an example

- ✓ Understand and accurately interpret iron studies using clinical examples of iron deficiency anaemia, anaemia of chronic disease and haemochromatosis
- ✓ Understand the common causes of leukopaenia (viral infections e.g. EBV)
- ✓ Understand the common causes of leukocytosis (bacterial infections e.g. Strep infections)
- ✓ Understand the common causes of thrombocytopaenia (ITP)
- ✓ Understand the common causes of thrombocytosis (acute phase reaction)
- ✓ Understand the clinical use of INR and PTT (anticoagulation therapy)
- ✓ Understand the role of the acute phase reactants - fibrinogen, prothrombin, factor VIII and platelets - in the development of DVT

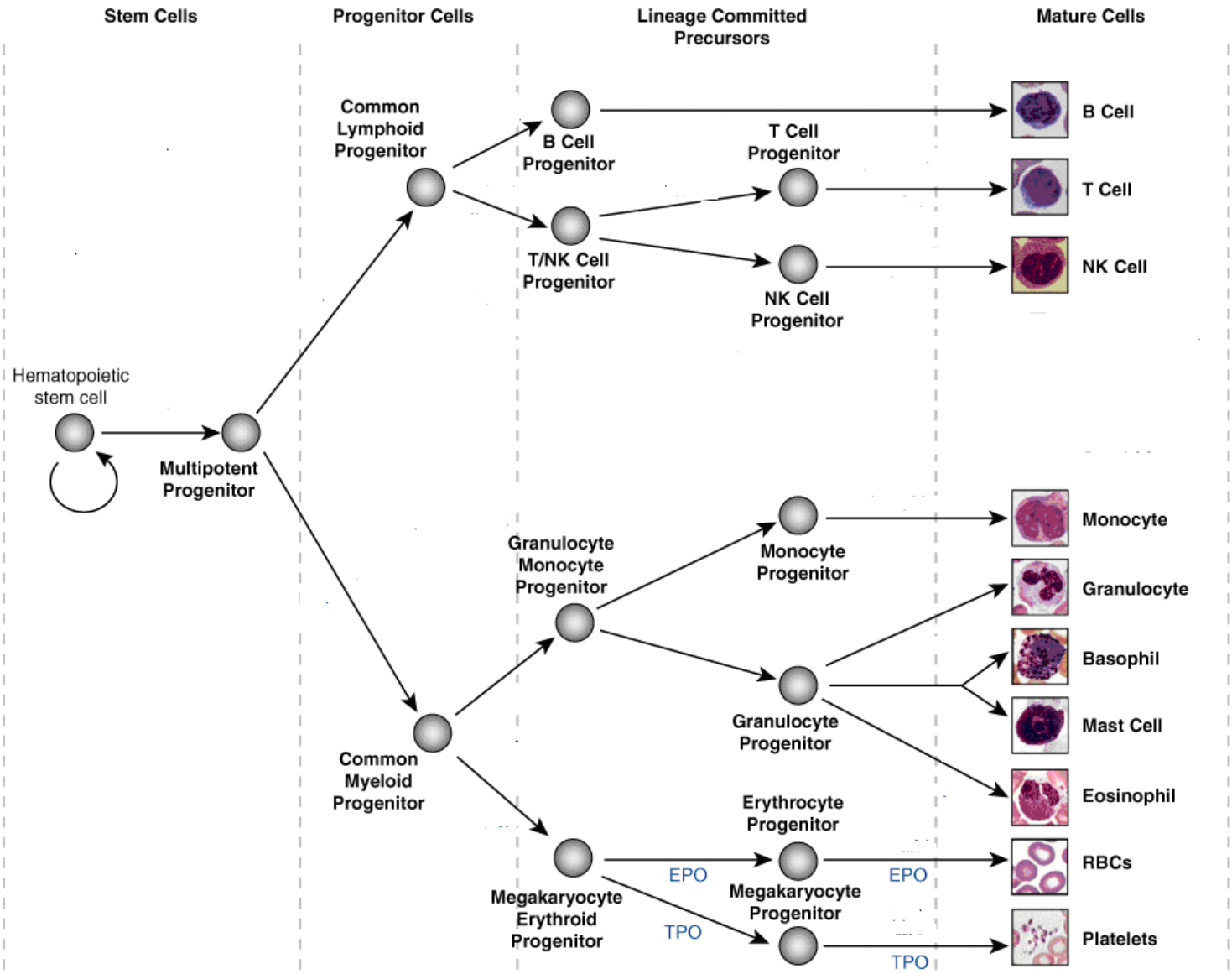
Important

- ➢ Understand the difference between round and oval macrocytes in macrocytic anaemia
- ➢ Understand the clinical relevance of Factor V Leiden (homozygous)

Desirable

- ✓ Understand the less common causes of polycythaemia: high altitude, cyanotic congenital heart conditions
- ✓ Understand the clinical effects of untreated/undiagnosed haemochromatosis on liver function, cardiac muscle, joints and pituitary gland.
- ✓ Understand the types of anaemias seen in patients with autoimmune conditions
- ✓ List the common conditions where anticoagulation therapy is indicated

Haemopoiesis



The Full Blood Count (FBC)

The full blood count gives us information about:

•**Red cells** (erythrocytes), including their ***indices*** and ***morphology***
•**White cells** (leukocytes), including the:

Total White Cell Count
and the
Differential Count - the proportionate numbers of cells which make up the total white cell count:
Neutrophils
Monocytes
Eosinophils
Basophils
Lymphocytes

•**Platelets,** including the ***total number*** and ***morphology*** of the platelets (young platelets are big platelets; adult platelet diameter 1 - 2μm)

Some of the more commonly encountered haematological disorders include:

Red cell Disorders

· ***Anaemia***	Haemoglobin level < lower limit of normal for age and sex
· ***Polycythaemia***	↑Red Cell Mass ↑ Haematocrit ↑ Haemoglobin

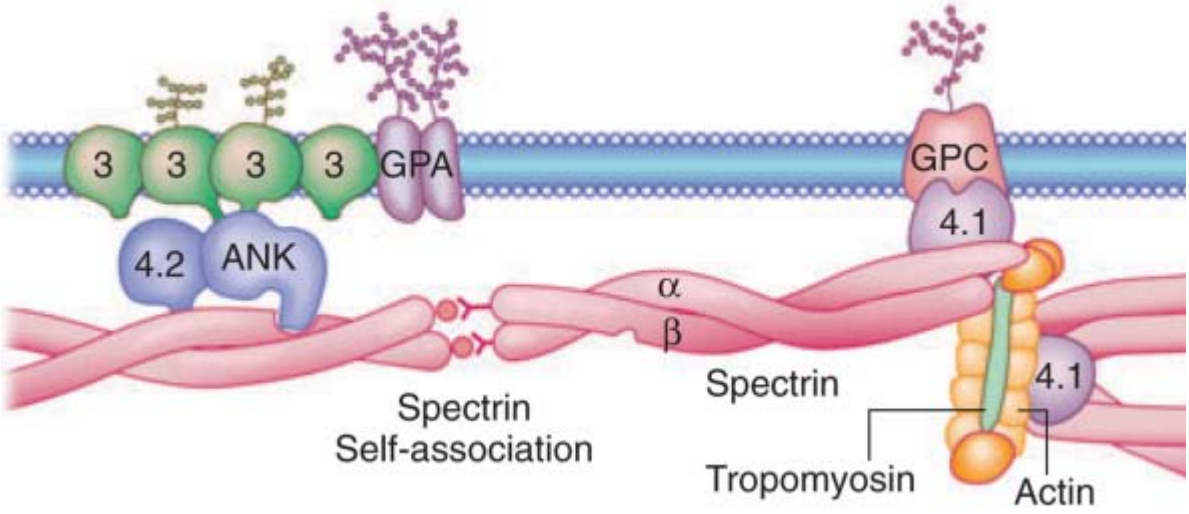
White Cell Disorders

· ***Non-neoplastic disorders***:	•*Leukopaenia* •*Leukocytosis*	
· ***Neoplastic disorders***:	•*Lymphoproliferative disorders:*	*Leukaemia* *Lymphoma*
	•*Myeloproliferative disorders:*	*Acute myeloid leukaemia* *Myeloproliferative syndromes* *Mylodysplasia*

Platelet Disorders

Affecting ***number*** of platelets: or ***function*** of the platelets	*Thrombocytopaenia / Thrombocytosis* example: Aspirin induced inhibition of platelet adhesion

Normal structure of the red cell membrane



Molecular binding interactions among the major proteins of the red cell membrane

ANK = ankyrin; GP = glycophorin.

The lipids of the red cell membrane consist mainly of phospholipid and cholesterol, with interspersed glycophorin and other proteins.

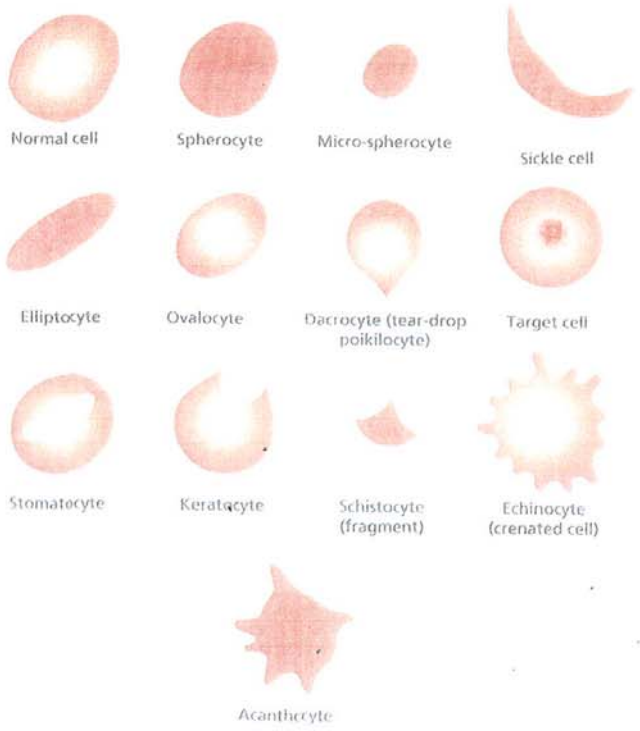
The deeper cytoskeleton, which is attached to the under surface of the membrane, is made up mainly of the proteins spectrin and actin.

Spherocytes and Poikilocytes

The structure of and interplay between these layers confers on the red cell its unique ability to deform, as it traverses the heart, blood vessels and spleen. The ratio between the amount of cell membrane (surface area) and contents of the red cell (volume) is critical; when the ratio is decreased, spherocytosis results, when the ratio is increased, stomatocytosis or target cells result.

Hereditary spherocytosis (HS) is a relatively common abnormality of red cells in individuals of northern European descent, with an incidence of 1/5000. It is usually transmitted as a dominant condition, but some cases (25%) are recessively inherited. The defect lies in the cytoskeleton, affecting either spectrin or ankyrin. The affected red cells have reduced deformability and lose membrane when they traverse the narrow passages in the splenic cords, and also when exposed to the high pressures and shearing forces as they travel through the circulation. When first formed in the marrow, HS red cells are morphologically normal, but as they lose progressively more membrane on their travels, they become spherical in shape.

Normal red cells become more fragile as they age. The membrane proteins denature as the cells age, and auto antibodies collect on the cell surfaces. This results in decreased deformability which causes them to haemolyse more readily than normal during their passage through the spleen. The splenic macrophages also damage the surface of the cells, as they phagocytose the Ag:Ab complexes situated thereon, and this also makes the cells more than usually fragile.



Spherocyte	Cell which is approximately spherical in shape so that it has lost its central pallor; the cell outline is regular
Microspherocyte	Spherocyte of reduced size and therefore diameter
Elliptocyte	Cell with an elliptical outline
Ovalocyte	Cell with an oval outline
Dacrocyte (tear-drop poikilocyte)	Cell shaped like a tear-drop
Target cell	Cell with a more strongly staining area in the centre of the area of central pallor
Stomatocyte	Cell with a central slit or stoma
Keratocyte	Cell with two or four curved horn-shaped projections
Schistocyte (red cell fragment)	Fragment of a cell, usually angular; a microspherocyte is a particular type of schistocyte
Echinocyte (crenated cell)	Cell with its surface covered with 20–30 small, regular, blunt projections
Acanthocyte	Cell with its surface covered with two to twenty projections of irregular shape and irregularly distributed
Sickle cell	Cell with a sickle or crescent shape, caused by the presence of a high concentration of an abnormal haemoglobin known as haemoglobin S

CLASSIFICATION OF ANAEMIA

Anaemias may be classified depending on the **mechanism** of their production or according to the **mean cell volume of the red cells.**

Mechanism	Examples
1.↓Production (bone marrow failure)	
▫Bone marrow aplasia/hypoplasia (empty marrow)	Aplastic anaemia Uraemia Hypothyroidism
▫Bone marrow infiltration (packed marrow)	Myelofibrosis 1º (myeloproliferative) Myelofibrosis 2 º to: metastases leukaemia esp. CML lymphoma myeloma
2. Defective RBC (bone marrow functioning but producing abnormal red cells)	
▫ Normal stem cells, haematinic deficiency:	Iron deficiency Iron unavailable – anaemia of chronic disease Vitamin B12/folate deficiency- megaloblastic anaemia
▫Abnormal stem cells	
•Acquired	Myelodysplasia
•Hereditary	Hereditary spherocytosis
3.↓Lifespan of RBC (marrow functioning and producing normal red cells)	
▫Blood loss	
▫Haemolysis	Acquired red cell defects e.g. from prosthetic heart valve

Classification of anaemia based on MCV

Volume of Red Blood Cells	Condition
1. Normocytic MCV 80 – 100 fl	Chronic disease (75% are normocytic) Chronic renal failure Haemorrhage Haemolysis BM hypoplasia BM infiltration
2. Microcytic MCV < 80 fl	Iron deficiency Chronic disease (25% become microcytic as the chronic disease progresses) Thalassaemia Sideroblastic anaemia (uncommon) Hyperthyroidism (uncommon)
3. Macrocytic MCV > 100 fl	Megaloblastic (oval macrocytes) Myelodysplasia Liver disease Hypothyroidism Haemolysis (↑↑reticulocytes)

* Alcohol is a very common cause of macrocytosis, with or without anaemia.

RED CELL INDICES

		Units	Ref Range
Hb	**(Haemoglobin)**	**g/L**	**(F 115 – 160)** **(M 120 – 180)**
RCC	**(Red cell count)**	**x 10^{12}/L**	**(F 3.8 – 5.2)** **(M 3.5 – 6.0)**
Hct /PCV	**(Haematocrit / Packed Cell Volume**		**(F 0.33 – 0.47)**
	= the proportion of blood occupied by erythrocytes)		**(M 0.35 – 0.51)**
MCV	**(Mean Corpuscular Volume = volume of red cells)**	**femtolitres (fL)**	**(80 – 100)**

***MCH (Mean Corpuscular Haemoglobin)**

***MCHC (Mean Corpuscular Haemoglobin Concentration)**

**Not routinely measured*

Please note: MCHC may be useful in microcytic anaemias

↑MCHC in Hereditary Spherocytosis (small dark cells)

↓ MCHC in Iron deficiency / Thalassaemia (small pale cells)

Some Common Anaemias

1. Iron deficiency (IDA)
2. Anaemia of chronic disease
3. Megaloblastic anaemia
4. Anaemia caused by haemorrhage
5. Anaemia of renal failure
6. Haemolytic anaemia

Iron Deficiency Anaemia

Iron deficiency anaemia is the most common type of anaemia worldwide; 30% of the world's population is anaemic, and half of these have iron deficiency.

Causes

▪ **Blood loss**
In adults, the cause is usually chronic blood loss, and **a source of bleeding must be established.** In premenopausal ♀, the cause is often ↑ menstrual loss. In other individuals, chronic blood loss from the GIT must be excluded, such as: Ca bowel, PUD, gastritis, NSAID/aspirin use, hookworm, angiodysplasia, inflammatory bowel disease, diverticulitis, polyps.

▪ **Rapid growth**
Stores may be inadequate during periods of ↑growth, such as the ↑growth rate in the teenage years, and in pregnancy (growing foetus)/infancy, exacerbated by prematurity and breast feeding.

▪ **Dietary deficiency**.
The diet may be deficient in iron. Good sources are meat, fish, cabbage, broccoli, peas, beans, iron-enriched cereals and bread.

▪ **Malabsorption of iron from GIT**
Iron may be ingested but inadequately absorbed from the GIT, a common cause being coeliac disease in children.

▪ **Haemosiderinuria**
An unusual cause of iron deficiency is loss of iron in the urine due to haemosiderinuria, from chronic intravascular haemolysis

Symptoms	*Signs*
Tiredness	Koilonychia
Pica	Cheilosis, including angular stomatitis
Pagophagia	
Dysphagia (Plummer-Vinson syndrome)	

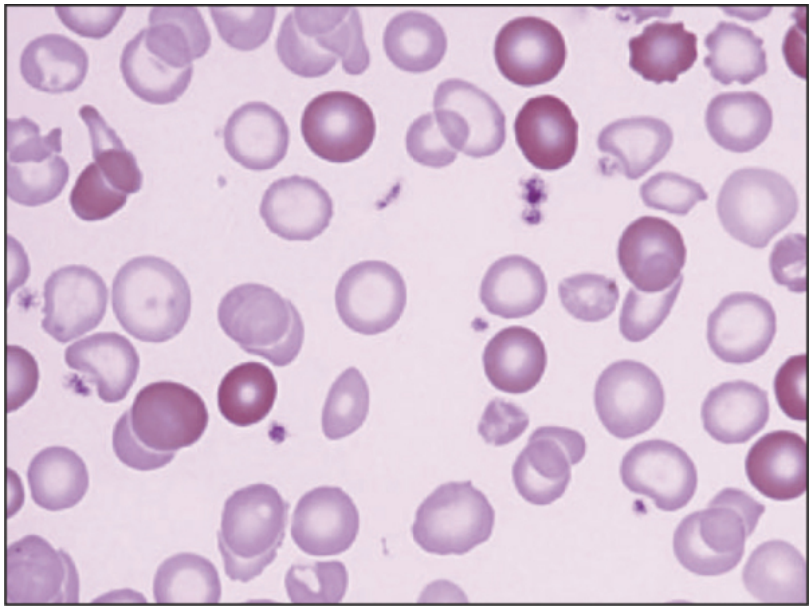
Investigations

•FBC

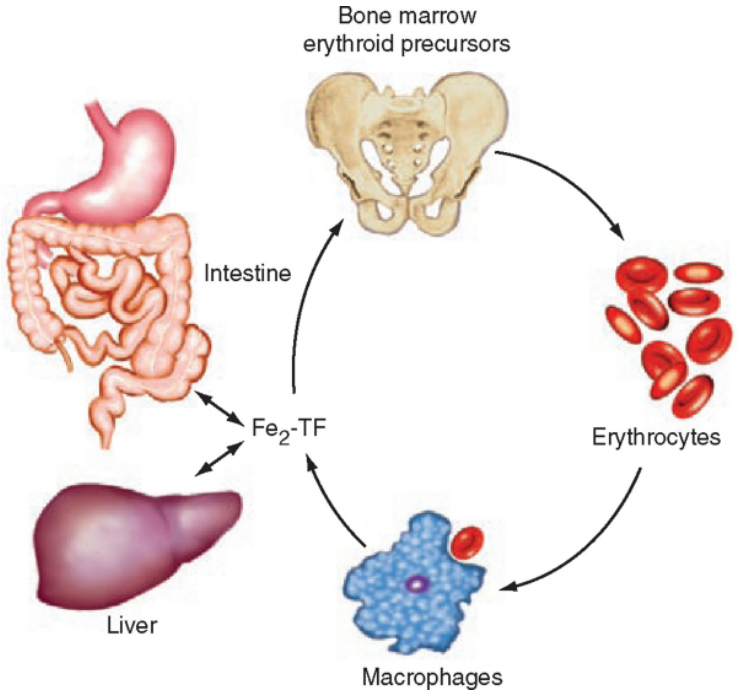
A microcytic anaemia is characteristic.	↓Hb ↓MCV
Hypochromic red cells	↓MCH ↓MCHC
Anisocytosis (variation in size).	↑RDW
Pencil and cigar poikilocytes are characteristically seen.	Pencil poikilocytes
A thrombocytosis is often present.	↑Platelets

• Iron studies

Serum Iron	↓	**µmol/L**	**10 - 30**
Transferrin	↑	**g/L**	**1.6 – 3.0**
Transferrin IBC	↑	**µmol/L**	**40 - 75**
Transferrin Saturation	↓	**%**	**15 - 45**
Serum Ferritin	↓	**µg/L**	**10 – 200**



Iron deficiency anaemia, post-transfusion. The cells are pale with an enlarged central pallor, in sharp contrast to the transfused normochromic cells. In this patient, many of the cells are not particularly microcytic, and a combined deficiency of iron, vitamin B12 or folate may be present.
This smear is an example of a dimorphic picture (two populations of cells)



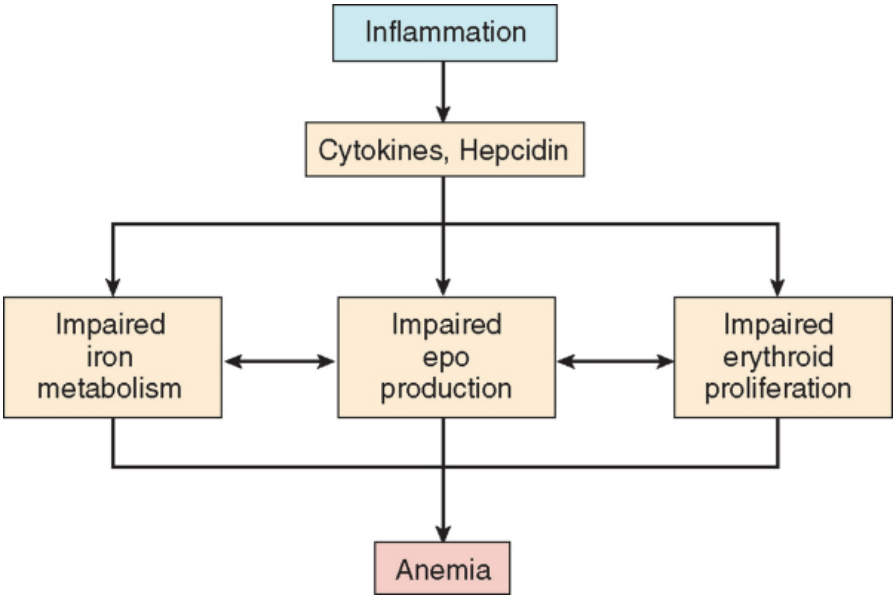
The iron cycle

Iron metabolism can be thought of as a closed loop involving circulating diferric transferrin (each molecule of transferrin carries 2x molecules of iron), the erythroid bone marrow, circulating erythrocytes, and reticuloendothelial macrophages. Most iron in the body can be found in this cycle.

A small amount is absorbed and lost through the intestinal mucosa.

Additionally, iron in excess of tissue needs is stored in the liver. For simplicity, other sites of iron use are not shown here. The most important of these is muscle, where iron is incorporated into myoglobin.

Anaemia of Chronic Disease



The anaemia of chronic disease occurs in inflammatory conditions, infection, tissue injury and malignancy, all of which have ↑levels of inflammatory cytokines and of the acute phase protein, hepcidin. The anaemia develops in part due to inadequate iron delivery to the marrow, in spite of normal or increased iron stores. The ferritin level is often increased 3x over basal levels, and is the most distinguishing feature differentiating this type of anaemia from true iron deficiency anaemia.

Cytokines

- inhibit release of erythropoietin (EPO) from the kidney
- suppress the response of the marrow to EPO
- promote haemolysis of senescent red cells
- promote release of hepcidin from the liver (acute phase response)

Cytokines → **↓ red cell production in marrow**
Cytokines → **↓ red cell survival**
Cytokines → **↑ hepcidin**

Hepcidin

Inhibits iron absorption from the intestine and inhibits iron transfer from marrow particles to developing erythrocytes and release of iron from other storage sites. These effects cause a fall in serum iron and poor haemoglobinisation of red cells.

Hepcidin → **↓ iron absorption**
Hepcidin → **↓ release of iron from stores**

Anaemia of renal failure

Anaemia of renal failure is caused by:

- ↓Erythropoietin production by the failing kidney
- Bone marrow suppression by toxic uraemic metabolites, and low levels of carnitine required for normal haemopoiesis
- Decreased red cell lifespan (lowgrade haemolysis) – cells affected by uraemic metabolites, cytokines and echinocytes have ↓lifespan
- Some patients who are on dialysis may develop iron deficiency occasioned by the dialysis procedure

Iron studies in Hypoproliferative Anaemias*

Tests	Iron Deficiency	Inflammation	Renal Disease
Serum Iron	↓	↓	Normal
Transferrin	↑	↓	Normal
TIBC	↑	↓	Normal
Saturation (%)	↓	↓	Normal
Serum ferritin (µg/L)	↓	Normal or ↑	Normal
Iron stores	0	2–4+	1–4+

Note: TIBC, total iron-binding capacity.

*Hypoproliferative anaemia = Reticulocyte count <2.5 % (low for degree of anaemia)

NORMAL VALUES

Iron Studies	Units	Ref Range
Serum Iron	**µmol/L**	**10 - 30**
Transferrin	**g/L**	**1.6 – 3.0**
Transferrin IBC	**µmol/L**	**40 - 75**
Transferrin Saturation	**%**	**15 - 45**
Serum Ferritin Assay	**µg/L**	**10 - 200**
MCV	**fL**	**80 – 100**
Marrow iron stores		**1 - 3+**

Megaloblastic Anaemia

Causes

- Folate deficiency
- Vitamin B12 (cobalamin) deficiency
- Myelodysplastic syndrome (refractory anaemia)
- Drugs: Anti-folate drugs e.g. Methotrexate
  Drugs which affect DNA synthesis e.g. Cytosine Arabinoside

The cause is usually deficiency of either Vitamin B_{12} or folate. The marrow is cellular, and the anaemia is based on ineffective erythropoiesis. The common feature of all megaloblastic anaemias is a defect in DNA synthesis that affects the rapidly dividing cells in the bone marrow.
Sources: Vitamin B12: animal products – meat, fish, dairy products
Folate: liver, yeast, spinach, other greens, mushrooms and nuts.

Clinical Features

Many asymptomatic patients are detected through the finding of a raised mean corpuscular volume (MCV) on a routine blood count.

The main clinical features in more severe cases are those of anaemia.

Anorexia is usually marked and there may be weight loss, diarrhoea, or constipation. Glossitis, angular cheilitis, a mild fever in the more severely anaemic patients, jaundice (unconjugated), and reversible melanin skin hyperpigmentation may also occur with deficiency of either folate or cobalamin.

Thrombocytopaenia and leukopaenia may occur. Patients are predisposed to infections, particularly of the respiratory or urinary tracts, and prone to bruising or bleeding.
Infertility is common in both men and women

Haematologic Findings

Oval macrocytosis, usually with anisocytosis and poikilocytosis, is the main feature. The MCV is usually >100 fL. Some of the neutrophils are hypersegmented (more than five nuclear lobes = right shift).

Leukopaenia and thrombocytopaenia are usually not severe.

Ineffective erythropoiesis → death of nucleated red cells in the marrow (intra-medullary haemolysis).

***Evidence for haemolysis**:*

Urine	**Blood**
↑Urobilinogen	↑Unconjugated bilirubin
Haemosiderinuria +ve	↓Haptoglobin level
	↑Lactate dehydrogenase (LDH)

Vitamin B12 Deficiency

Causes:

▫ Nutritional	Vegans
▫ Autuimmune	Pernicious anaemia
▫ Gastric causes	Gastrectomy (partial/total)
	Congenital deficiency of intrinsic factor
▫ Intestinal causes	Crohn's disease
	Tropical sprue
	Fistula, blind loop, stricture, ileal resection

Actions of vitamin B12

Vitamin B_{12} (Cyanocobalamin)

Found in meat and animal protein. (The elderly may not be capable of extracting the Vitamin B_{12} from food, but may be able to utilise it in its pure form if given orally.)

Several forms:	Methylcobalamin	a cofactor in DNA synthesis
	Adenosylcobalamin	helps to repair myelin sheaths

Deficiency of Vitamin B_{12} results in a combination of effects on the nervous system:

◦Brain:	Lesions in the white matter (→ dementia)
◦Peripheral nerves:	Degeneration of myelin sheaths
◦Spinal Cord:	Lesions of cortico-spinal tracts and posterior columns

Pernicious anaemia (PA)

PA may be defined as a severe lack of IF due to gastric atrophy. It is a common disease in north Europeans but occurs in all countries and ethnic groups. IF is required for absorption of vitamin B12 in the ileum.

The disease occurs more commonly in close relatives and in persons with other autoimmune diseases, e.g. thyroid diseases, vitiligo, hypoparathyroidism, and Addison's disease. It is also associated with hypogammaglobulinaemia, with premature graying or blue eyes, and in persons of blood group A
The life expectancy is normal in women once regular treatment has begun. Men have a slightly subnormal life expectancy as a result of a higher incidence of carcinoma of the stomach

Investigations

◦ **S-Vitamin B12** level to confirm diagnosis, as well as s-Folate level and Iron studies, as a mixed deficiency may be present.

◦ **Gastric Biopsy** shows atrophy of all layers and an absence of parietal and chief cells

◦ **Antibodies**

Intrinsic Factor (IF) antibody:
Two types of this antibody may be found in the sera of patients with PA.
· "Blocking," or type I, antibody prevents the combination of IF and vitamin B12
· "Binding," or type II, antibody prevents attachment of IF to ileal mucosa.

Parietal cell antibody
Present in the sera of almost 90% of adult patients with PA but is not specific for PA.

Treatment of Vitamin B12 deficiency

· **Vitamin B_{12} injections**	(1000 µg weekly for 1 month, then monthly thereafter)
· **Intranasal vitamin B_{12}**	
· **Oral vitamin B_{12}**	(1000 µg daily) for nutritional deficiency

When treatment is commenced for a megaloblastic anaemia induced by vitamin B12 deficiency, or a mixed deficiency of vitamin B12 and folic acid, the patient should first receive a loading dose of vitamin B12 before folic acid treatment is commenced, to prevent precipitation of subacute combined degeneration of the cord. (In a mixed deficiency, if folate alone is given, the marrow may respond by increasing erythropoiesis thus utilising the last remaining amount of vitamin B12, and causing SACDC)

Folate Deficiency

Causes

- Dietary
- Intestinal malabsorption
- Excess utilisation or loss

Physiologic
Pregnancy and lactation, prematurity
Pathologic
Chronic haemolytic anaemias
Malignant diseases:
Inflammatory/infective diseases: e.g.TB

Actions of Folate

Folic Acid (Pteroylglutamic acid)
Present in many plant & animal foods, especially leafy green vegetables, mushrooms, yeast & liver.

Actions:
1. Coenzyme in reactions involving 1-carbon unit transport, as in nucleotide synthesis
2. Amipo acid conversions (formation of an amino acid from another amino acid)
3. Generation & use of formate

*Conversion of homocysteine to methionine, this reaction requiring vitamin B12 as cofactor

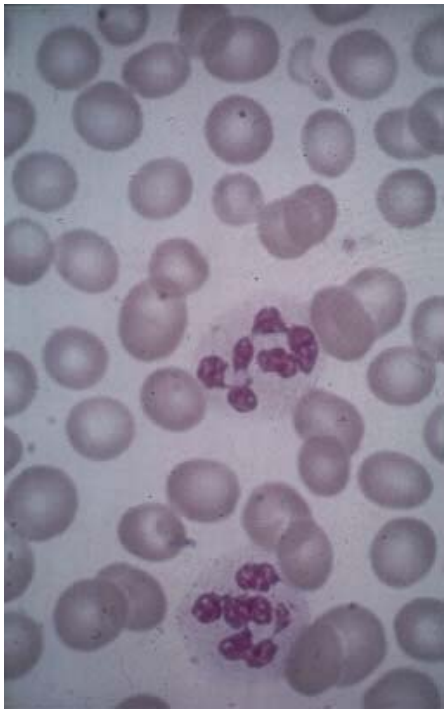
Investigations

S-Folate, (Red cell folate), S-Vitamin B12, Iron studies

Treatment

Folic acid 1 – 2mg orally daily

Peripheral blood smear in megaloblastic anaemia, showing hypersegmented neutrophils & oval macrocytes



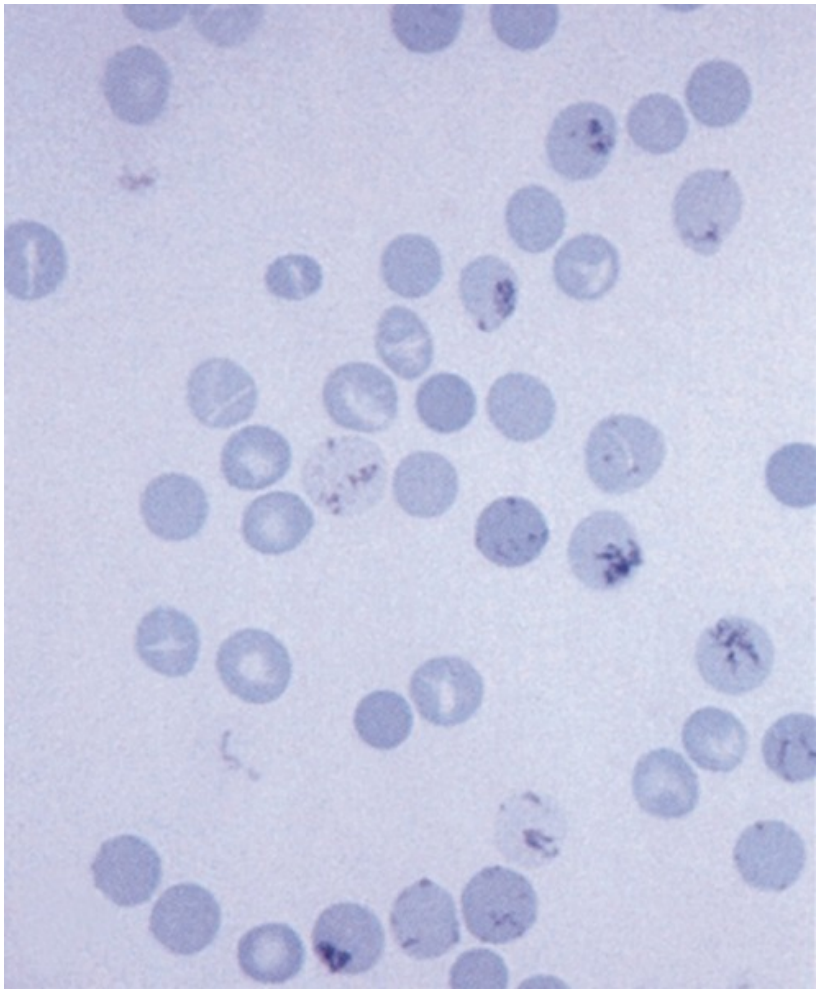
Anaemia caused by acute haemorrhage

Causes
- Trauma to a large blood vessel
- Erosion of an artery by e.g. peptic ulcer or neoplasm
- Failure of normal haemostasis

Sudden loss of ⅓ blood volume may be fatal, whereas more gradual loss of ≤ ⅔ total blood volume over 24 hours may still be compatible with life.

Symptoms and signs (due to acute loss of blood volume and hypoxia):
Faintness, thirst, sweating, tachycardia, tachypnoea, postural hypotension (initial ↑BP due to vasoconstriction may occur); subsequent sustained hypotension and death.

Laboratory findings
During and immediately following acute haemorrhage, the red cell count (RCC), Haemoglobin (Hb) and haematocrit (Hct) may be relatively normal due to vasoconstriction.
Within a few hours, tissue fluid enters the circulation → haemodilution and ↓RCC, ↓Hb and ↓Hct.
The anaemia is normocytic. Leukocytosis and thrombocytosis may occur.
Several days later, reticulocytes start to appear in the peripheral blood. If the haemorrhage was massive, early red cells (normoblasts) and white cells (left shift) may be seen = leukoerythroblastic blood picture, indicative of marrow response to the blood loss.



Reticulocytes with reticular material after methylene blue staining

HAEMOLYTIC ANAEMIA

Haemolysis may occur *intravascularly or extravascularly* (mainly in the spleen).
The majority of cases of haemolysis occur extravascularly; often a combination of intravascular and extravascular haemolysis takes place simultaneously.
Haemolytic anaemias may be classified according to whether *the red blood cells are intrinsically normal or abnormal.*

Red Blood Cell Intrinsically Normal

Some factor is affecting *normal red cells*, causing haemolysis. These factors include trauma, antibodies, toxins, parasites, venoms, copper, hypersplenism

Trauma	Fibrin strands in DIC/TTP/HUS (microangiopathic haemolytic anaemia) Prosthetic heart valves (especially aortic) and aortic sclerosis Karate chops / "March" haemoglobinuria e.g. marathon runners/bongo drumming Severe burns (spectrin denatures)
Antibody	Auto-antibody: Warm = IgG Cold = IgM Iso-antibody e.g .Incompatible blood transfusion / Rhesus incompatibility
Bacterial infection	Clostridium perfringens & Welchii, Streptococcal, Staphylococcal, Meningococcal & *Bartonella henselae (Cat scratch disease) infections
Parasite	Malaria, Babesia, *Bartonella bacilliformis (Oroya Fever)
Venom	Cobra
Copper	Wilson's Disease
Hypersplenism	e.g. Portal hypertension

Red Blood Cell Intrinsically Abnormal

Membrane	Hereditary Spherocytosis Paroxysmal Nocturnal Haemoglobinuria	
Intracellular	Enzyme deficiency	e.g. G6PD deficiency
	Haemoglobin is abnormal	e.g. Thalassaemia Sickle cell anaemia

*Bartonella henselae causes an immune haemolysis
*Bartonella bacilliformis parasitizes the red cells causing haemolysis

Coombs test

The direct Coombs test. This is an anti-globulin test that identifies antibodies *attached to red cells*, and which are causing haemolysis (i.e. an antibody to an antibody). The added antibody causes visible agglutination of the RBCs. This is the *direct Coombs test.*

The indirect Coombs test identifies *circulating* antibodies to red cells, that is, those which are *not attached to red cells,* as in post pregnancy and ABO antibodies. A positive test does *not* indicate a haemolytic process.
In this test, the patient's plasma, containing the circulating, non-attached antibodies, is incubated with RBCs whose antigens are known; the Coombs reagent (antibody to patient's antibody) is added and if the patient's antibodies have attached to the known antigens on the test RBCs, agglutination will take place, and the antibodies may thus be identified.

Laboratory findings

In brisk, intravascular haemolysis

In blood:
↑Reticulocyte count ± normoblasts
Unconjugated hyperbilirubinaemia
↑LDH
↓Haptoglobin

In Urine:
↑Urobilinogen
Haemoglobin
Haemosiderin

*Methaemalbuminaemia – free haemoglobin becomes oxidized to the ferric form (MetHb); the methaem dissociates from the globin and binds to albumin, forming methaemalbumin.
*↓Haemopexin - a protein which binds free Hb once haptoglobin is saturated.

*Haemoglobinaemia
*Not routinely measured

In extravascular haemolysis

In blood:
↑Reticulocyte count
Unconjugated hyperbilirubinaemia
± ↓Haptoglobins

In Urine:
↑Urobilinogen
No haemoglobinuria or haemosiderinuria

Usually no haemoglobinaemia, methaemalbuminaemia, ↓haemopexin

Sequelae of chronic haemolysis:
Pigment gallstones (↑bilirubin in bile)
Folate deficiency (All available folate used up by erythropoeisis trying to keep pace with haemolysis)
Iron deficiency in chronic intravascular haemolysis (iron lost via haemosiderinuria)
Iron overload in chronic extravascular haemolysis.(↑absorption for ↑erythropoiesis in an attempt to keep pace with haemolysis)

Miscellaneous

•In Hereditary Spherocytosis, the defect is in the cytoskeleton of the RBC, the spectrin and ankyrin proteins, preventing deformability of the RBC.

*RBC diameter ~ 7 μm; needs to get through 2 μm diameter in the spleen. If the red cell cannot deform to enable it to squeeze through the narrow spaces in the spleen, little bits of the cell membrane get phagocytosed by splenic macrophages and this results in a small, dark red cell – the spherocyte.
*Nucleus of small lymphocyte = 8 μm in diameter

•RBC travels 480km in its 120 day life, that is, 4km/day

•Chromium-labelling of red cells allows lifespan of red cells to be determined & the site of their destruction

Autoimmune Haemolytic Anaemia

The antibody causing the haemolysis may be IgM or IgG

If the antibody *avidly* fixes complement, *intravascular* haemolysis may occur
If the antibody *weakly* fixes complement, *extravascular* haemolysis is more likely.

80%	Warm, when the antibody is reactive at	37 ° C = IgG
20%	Cold, when the antibody is reactive at	4 ° C – 30 ° C = IgM

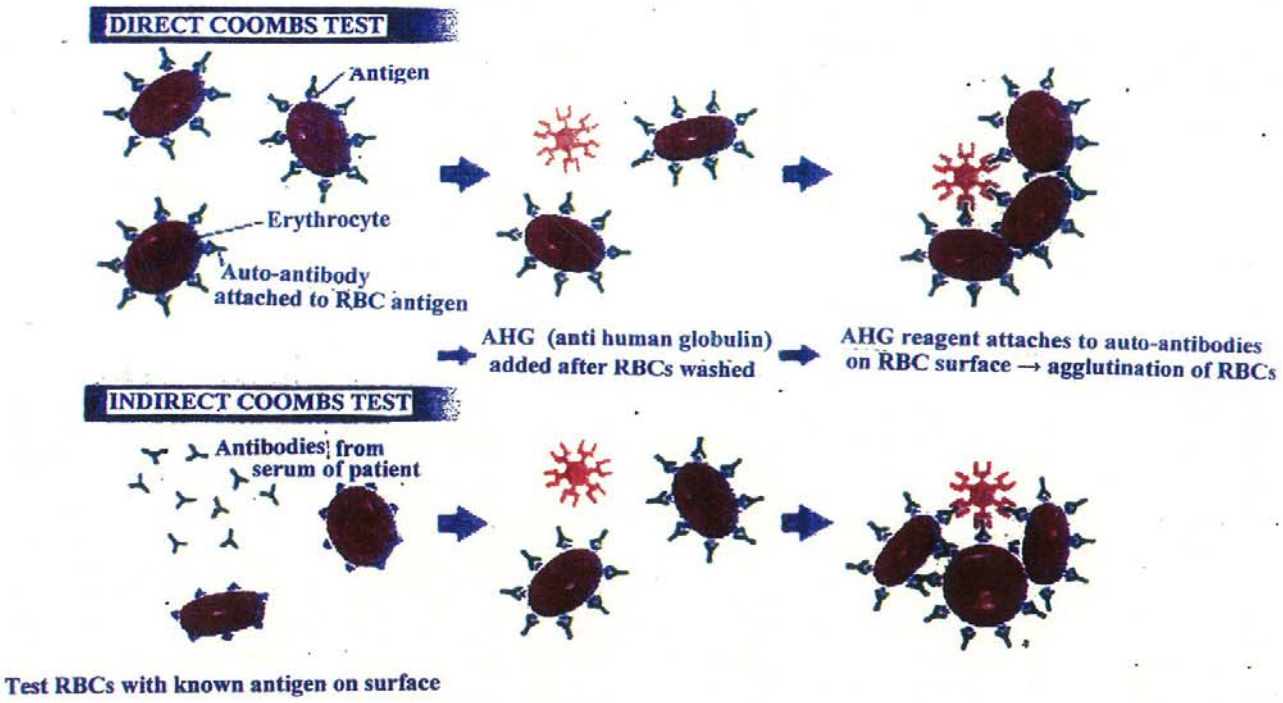
Warm

1. Idiopathic in 50%
2. Lymphoproliferative conditions (B cell) e.g. lymphoma
3. Solid tumours — lung, colon, kidney, thymus
4. CT diseases — SLE, RA etc
5. Drugs — methyldopa, penicillin
6. Miscellaneous — ulcerative colitis, HIV infection

Cold

Mostly in the elderly patient with lymphoma → acrocyanosis
Occasionally Infectious Mononucleosis, Mycoplasma pneumonia

Coombs test will be positive.



Anaemia in Liver Disease

1. Nutritional – folate / Vitamin B12 deficiency
2. GIT blood loss - chronic → iron deficiency
   - acute example: oesophageal varices
   (Coagulopathy due to ↓production of clotting factors and ↓Vit K absorption)
3. Direct toxic effect on the bone marrow by alcohol
4. Hypersplenism (portal hypertension)
5. Haemolysis – acanthocytosis
   - hypercholesterolaemia (obstructive jaundice)

Anaemia in Uraemia

1.↓ Erythropoietin
2 Direct toxic effect of "uraemic toxin/s" on bone marrow
3. Haemolysis – also direct toxic effect of "uraemic toxin/s"

2 and 3 improve with dialysis

Anaemia in Hypothyroidism

1. Absence of thyroid hormone can → bone marrow suppression, even aplasia
2. Hypercholesterolaemia → macrocytes with/without haemolysis
3. Menorrhagia → iron deficiency
4. Associated pernicious anaemia (Hashimoto's is also autoimmune)
5. Folate is poorly absorbed from GIT

POLYCYTHAEMIA (ERYTHROCYTOSIS)

True
/
\
Spurious

True Polycythaemia

Primary / Secondary

Primary = Polycythaemia Rubra Vera, a myeloproliferative disease

Secondary = Polycythaemia in response to ↑ *level of erythropoietin*, which may be *appropriate*, as occurs in hypoxic states.

Example: Cyanotic congenital heart disease
COPD
Living at high altitude

or

Inappropriate ↑ level of erythropoietin:

•Some malignant tumours secrete EPO.

Example: Renal cell carcinoma
Hepatoma

•Some athletes take EPO inappropriately and develop secondary erythrocytosis.

Spurious Polycythaemia

Occurs in dehydration, when there is a ↓ in plasma volume

•Plasma volume studies are not done at TTH

•The JAK test (Janus kinase test) is a molecular biology test which differentiates primary from secondary polycythaemia. It identifies the chromosomal abnormality which is present in all cases of Polycythaemia Vera.

Disorders of white cell numbers

(excluding the leukaemias)

Leukopaenia - a decrease in the total number of leukocytes to below the lower limit of normal

***White Cell Count Reference range:** **$4 - 11 \times 10^9$/L**

The reduction in the count may be due primarily to a fall in the granulocyte count (granulocytopaenia) or in the lymphocyte numbers (lymphopaenia)

Leukopaenia → **Granulocytopaenia**
Leukopaenia → **Lymphopaenia**

Granulocytopaenia, the most important being neutropaenia

Neutropaenia is present when the neutrophil count < 2.0×10^9/L (particularly dangerous when level falls to < 0.5×10^9/L)
This predisposes the individual to infection, which may be severe enough to result in death.

Causes:

- ↓Production of neutrophils - all the causes of bone marrow failure, such as:
  - Aplastic anaemia
  - Chemotherapy
  - Other Drugs
  - Myelophthisic anaemia
- Ineffective neutrophil production
  - Megaloblastic anaemia
- ↑Destruction of neutrophils
  - Immune mechanisms
  - Hypersplenism

Lymphopaenia

Lymphocyte count < 1.0×10^9/L

Causes:
- Congenital immunodeficiency syndromes
- HIV
- Corticosteroids

Leukocytosis – an increase in the number of leukocytes above the upper limit of normal. This increase may primarily due to an increase in the granulocytes (granulocytosis) or in the lymphocytes (lymphocytosis)

Leukocytosis / \ **Granulocytosis** / **Lymphocytosis**

Granulocytosis

Neutrophilia
- Pyogenic infections
- Inflammatory conditions e.g. Myocardial infarction, Burns

A *leukaemoid reaction* occurs when an extremely high white cell count, which is left shifted (immature forms in peripheral blood), occurs in response to infection or bone marrow infiltration, and may be confused with a leukaemia. The leukocyte alkaline phosphatase (LAP) of these leukocytes is ↑, whereas in chronic myeloid leukaemia, the LAP is ↓ and Philadelphia chromosome positive.

Eosinophilia
- Allergy
- Parasites
- Drug reactions
- Malignancies e.g. Hodgkin's disease
- Autoimmune diseases

Basophilia Myeloproliferative diseases e.g. CML (Chronic myeloid leukaemia)

Monocytosis

Chronic infections	e.g. TB
Autoimmune diseases	
Inflammatory bowel disease	e.g. Ulcerative colitis

Lymphocytosis

Lymphocytosis accompanies monocytosis in states of chronic immunologic stimulation

e.g. TB
- Bacterial endocarditis
- Autoimmune diseases
- Viral infections, such as:
  - Infectious mononucleosis
  - Hepatitis A
  - CMV infections
  - Pertussis

PLATELETS

Structure

Platelets are membrane-bound smooth discs 2 – 4 μm in diameter and are formed from megakaryocytes in the bone marrow.

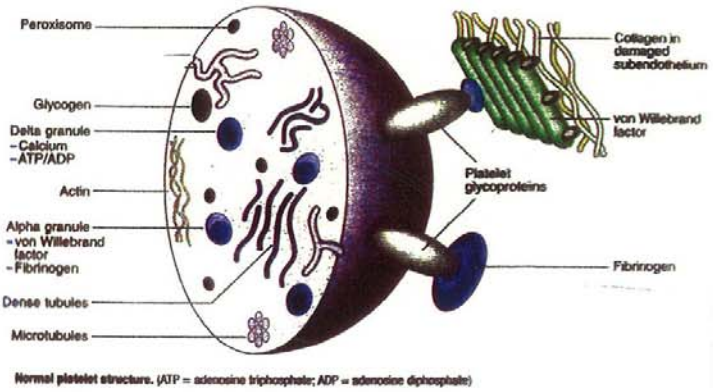
They have 2 types of glycoproteins on the surface, one of which attaches to von Willebrand factor which forms a secure bridge between the platelet and the exposed collagen of the blood vessel.
The other glycoprotein acts as a receptor for fibrinogen which forms a bridge between adjacent platelets helping to form the platelet plug.

Inside the platelet are 2 x types of granules:

α granules contain:
- Fibrinogen
- Factor V
- Factor VIII
- Platelet factor 4
- Growth factors

δ granules contain:
- ADP/ATP
- Calcium
- Histamine
- Serotonin
- Epinephrine

NORMAL PLATELET STRUCTURE



Normal platelet structure. (ATP = adenosine triphosphate; ADP = adenosine diphosphate)

When platelets come into contact with exposed sub-endothelial collagen, 3 things happen:

Platelet adhesion
Von Willebrand factor anchors the platelet to the collagen forming a strong bond

Secretion
◦Both types of granules release their contents

◦A phospholipid complex appears on the surface of the platelet which acts as a binding site for calcium and clotting factors involved in the intrinsic pathway

◦Thromboxane (TXA2) is manufactured inside the platelet from arachidonic acid, which is derived from platelet membrane phospholipid.

Aggregation
TXA2, ADP and thrombin act together to stimulate platelet aggregation. They do this by changing the conformation of the glycoprotein receptor on the platelet surface, facilitating the binding of fibrinogen to the receptor.
Fibrinogen binds platelets to each other forming a big group of platelets.

The next step is activation of the coagulation cascade, which results in formation of fibrin which cements the platelet plug.

Thrombocytopaenia

Causes: **Central (bone marrow)** / \ **Peripheral (peripheral blood)**

Central Bone marrow failure

Peripheral •↑Destruction of platelets
- Immune
- Drug – induced
- Hypersplenism

•↑Consumption of platelets:
- DIC
- TTP (enzyme deficiency→↑von W f)
- HUS (E.Coli toxin→endothelial damage)
- *Heparin-induced thrombocytopaenia

•Massive blood transfusion using old blood (platelets senescent)

*3 – 5 % of patients treated with Heparin develop this condition, which → severe morbidity due to limb/tissue ischaemia, even death. This is an autoantibody reaction to Heparin-platelet factor 4 complex which is situated on the platelet surface. This reaction (Ag-Ab reaction) promotes platelet aggregation → widespread thrombus formation and consumption of platelets → thrombocytopaenia. It does not appear to occur to any extent with fractionated heparin usage.

Thrombocytosis

An increase in the platelet count can be caused by a number of conditions:

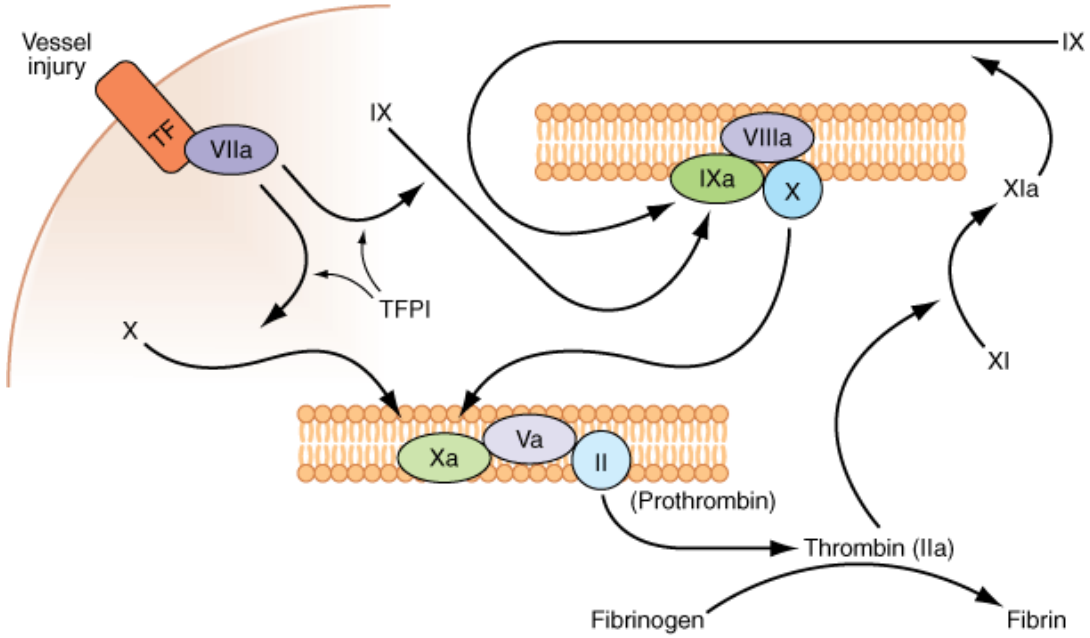
Essential (primary)

- Essential thrombocytosis (a form of myeloproliferative disease)
- Other myeloproliferative disorders such as chronic myeloid leukemia, polycythemia vera, myelofibrosis

Reactive (secondary)

- Inflammation – acute phase reaction
- Post splenectomy (decreased breakdown of platelets)
- Hemorrhage and/or iron deficiency

Coagulation



Coagulation is initiated by tissue factor (TF) exposure, which, with factor (F)VIIa, activates FIX and FX, which in turn, with FVIII and FV as cofactors, respectively, results in thrombin formation and subsequent conversion of fibrinogen to fibrin. Thrombin activates FXI, FVIII, and FV, amplifying the coagulation signal. Coagulation requires calcium (not shown) and takes place on phospholipid surfaces, usually the activated platelet membrane.

Extrinsic pathway: Initiated by activation of FVII by TF

Intrinsic pathway: Initiated by activation of FIX by FVII:TF complex or by FXIa (FXI activated by FXIIa, or by thrombin)

Common pathway: Initiated by activation of FX → FXa which, together with FVa, platelet factor 3 and FIV (calcium), then activates prothrombin

The extrinsic pathway is explosive taking only 15 seconds to produce a clot. Once thrombin has been formed, the reaction proceeds much faster, as thrombin then activates factor V.

The intrinsic pathway is more sedate, taking 1 – 6 minutes to form a clot.

There are interactions between the two pathways:

•**Tissue thromboplastin** (factor III) being involved in the activation of factor IX (intrinsic pathway), VII (extrinsic pathway), and II (common pathway).

•**Factor VII** (extrinsic pathway) helps to activate factor IX (intrinsic pathway).
In fact, factors XI and XII are not really required in the system at all, and their deficiency produces a very mild, if any, bleeding disorder.

Factors V and *VIII* are lysed by Protein C and S. Factor V Leiden is a relatively common genetic disorder affecting Factor V, such that it is resistant to lysis by protein C and S, and predisposes therefore to thromboembolism
Lack of *Factor VIII* → Haemophilia A
Lack of *Factor IX* → Haemophilia B (Christmas disease)
Lack of *Factor VIII RAG* (*von Willebrand Factor*) → von Willebrand's disease
(RAG = related antigen)
Factor VI is non-existent

Thrombin

Thrombin has several functions:
- To promote clotting
- To limit the clotting process

Actions which promote clotting:

- Stimulates platelet aggregation
- Activates Factors I, V, VIII, XIII

Inhibition of clotting:

When fibrin is formed, thrombin is adsorbed on to the fibrin, preventing thrombin from wandering off into the circulation causing widespread thrombus formation.

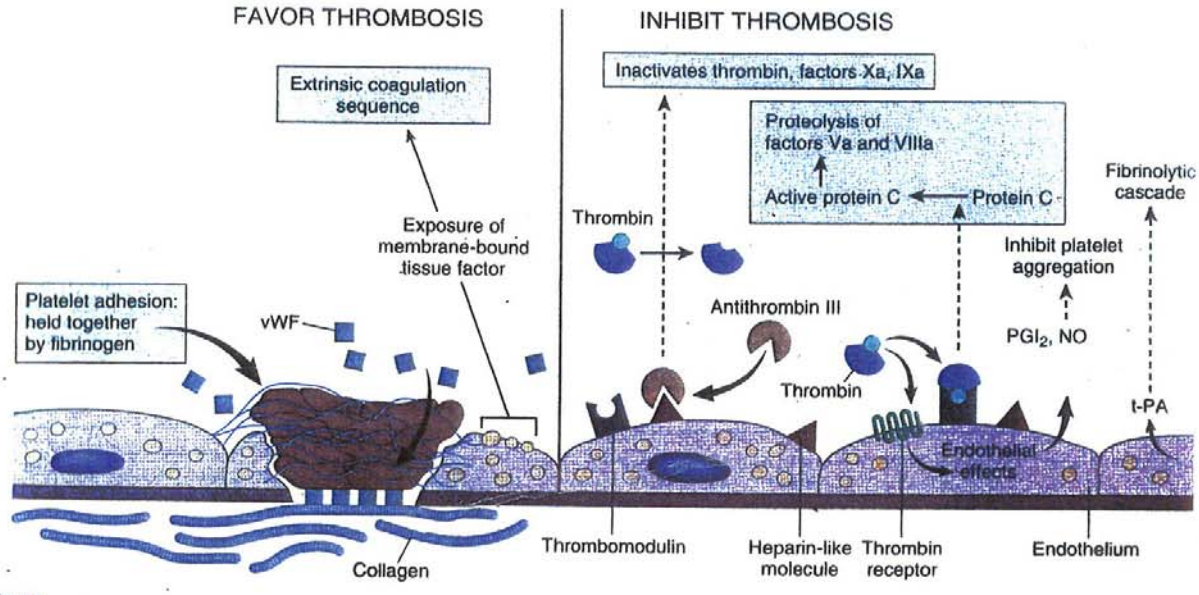
When thrombin binds to thrombomodulin on the endothelial cell, Protein C is activated to lyse Factors V and VIII, ably assisted by protein S

Other mechanisms which limit the coagulation process

Anti-thrombin III (ATT) – heparin complex inhibits thrombin, Factors IX, X

Fibrinolytic pathway:
Factor XII and plasminogen activators convert plasminogen to plasmin, which lyses fibrin. This results in production of fibrin degradation products, which will be elevated in cases of thromboembolism.

PGI_2 (prostacycline) *and NO* (nitrous oxide) inhibit platelet aggregation



Figure

Schematic illustration of some of the pro- and anticoagulant activities of endothelial cells. Not shown are the pro- and antifibrinolytic properties (see text). NO, nitric oxide; PGI_2, prostacyclin; t-PA, tissue plasminogen activator; vWF, von Willebrand factor.

Warfarin

Vitamin K is found in many foodstuffs including vegetables (spinach, cauliflower, cabbage), and dairy products; it is also synthesized by colonic bacteria.

It is fat soluble, requiring the presence of bile in the gastrointestinal tract for its absorption.

Its absorption therefore decreases:

In liver disease (→inadequate production of bile)
Bile duct obstruction
Intestinal disease
Antibiotic Rx → sterilization of the bowel.

It is required for the carboxylation of clotting factors II, VII, IX and X which converts them from an inactive to an active form.

Proteins C, S and Z are also Vitamin K dependent.

Warfarin inhibits the reductase enzymes which replenish the active form of Vitamin K after it has been used in the carboxylation of the clotting factors.

The half-lives of the vitamin K dependent clotting factors are:

Factor VII	6 hours
Factor IX	20 hours
Factor X	40 hours
Factor II	60 hours

Thus, after the initial dose of Warfarin, there will be a delay of 24 – 36 hours before it can take effect, as these factors may already be activated and will need to be metabolised.

Heparin

Commercial unfractionated heparin (UFH) derived from ox and pig, consists of sulfated polysaccharides. Heparin attaches to ATT (anti-thrombin 3) to form a complex

Heparin — Anti thrombin 3
↓ inhibits
Thrombin, IX, X

Low molecular weight heparins (LMWH) are obtained by cleaving UFH → smaller units. These are more active against factor X than against thrombin. They do not cause HIT (heparin induced thrombocytopaenia) as frequently as UFH.

Warfarin efficacy is tested by the Prothrombin Time (PT) and reported as the INR (International normalised ratio). This is the ratio of the patient's PT to a normal control PT, standardised thromboplastin having been used in the tests.

Heparin efficacy is tested by the Partial Thromboplastin Time (PTT)

Normal ranges:

INR **0.9 – 1.2**

PT **10 – 13 seconds**

PTT **26 – 41 seconds**

Prothrombin Time (PT) tests integrity of the extrinsic (and common) pathways (factors II, V, X, VII). The reagent used is placental or recombinant thromboplastin.

Partial Thromboplastin Time (PTT) tests integrity of the intrinsic (and common) pathways (factors II, V, X, VIII, IX, XI, XII). Reagents used: silica, phospholipids (derived from animal tissue, & Ca++

Thrombin Time tests the efficacy of fibrin production from fibrinogen

Exogenous thrombin is added to the specimen & time taken for clot formation. It is a direct test of fibrinogen function. Prolongation occurs if fibrinogen is ↓/ mal-functional (dysfibrinogenaemia)

Thrombin

↓

Fibrinogen → Fibrin

Indications for anticoagulation therapy

Heparin:
- Venous thromboembolism treatment
- Unstable angina
- Acute myocardial infarction
- Coronary angioplasty
- Surgery requiring cardiopulmonary bypass
- Other high-risk patients undergoing surgery

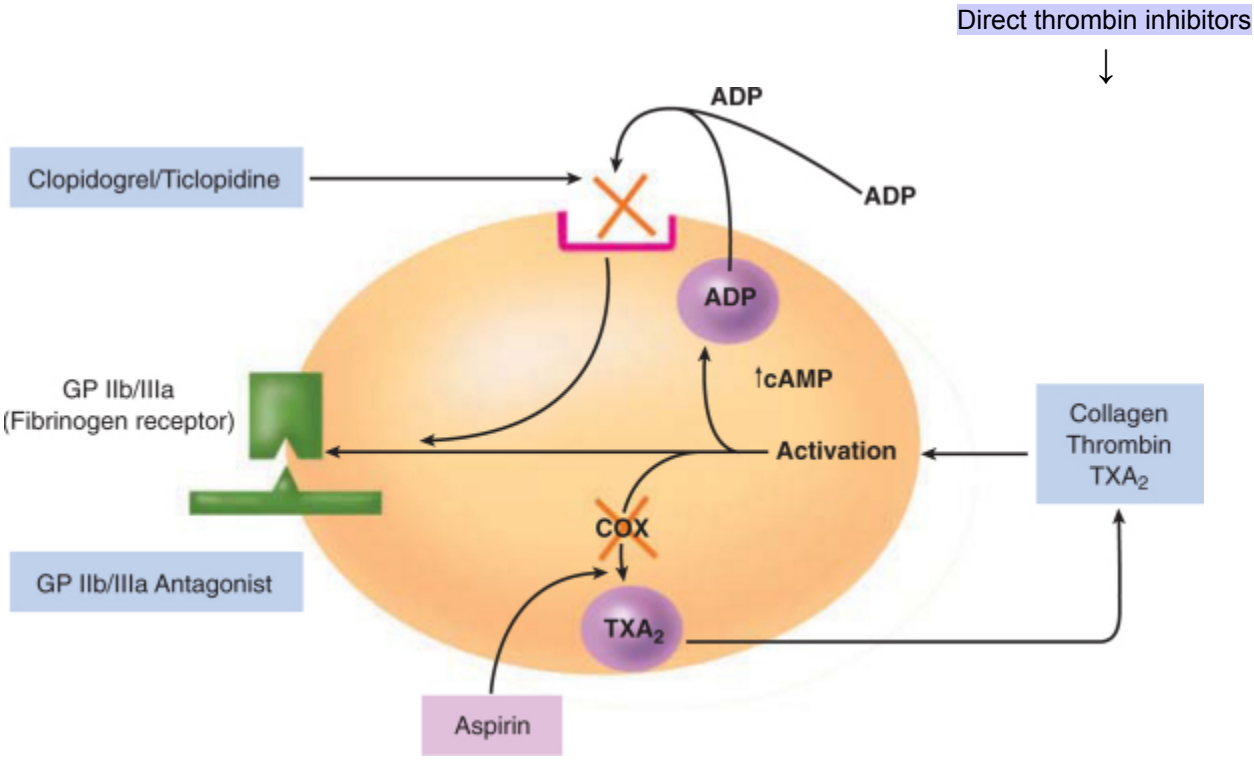
Warfarin:
- Deep venous thrombosis (DVT) treatment/prophylaxis
- Pulmonary embolism (PE)
- Prosthetic heart valve
- Atrial fibrillation
- Ischaemic stroke
- Post acute myocardial infarction

Aspirin:
- Myocardial infarction prophylaxis
    - Patients at risk for a coronary event
    - Patients with stable coronary artery disease
- Coronary angioplasty to prevent re-stenosis and thrombosis
- In combination with warfarin
    - Mechanical prosthetic heart valves
    - Atrial fibrillation

Clopidogrel: Oral anti-platelet drug which acts by irreversibly modifying the platelet receptor for ADP, thus preventing platelet aggregation in response to ADP.
- Atrial fibrillation
- CVA/TIA
- STEMI
- ACS
- PVD

Direct thrombin inhibitors:	prevent conversion of fibrinogen to fibrin
Glycoprotein inhibitors:	block binding of fibrinogen onto the glycoprotein receptor site on the platelet

Mechanisms of action of anti-platelet therapies



ADP = adenosine diphosphate

cAMP = cyclic adenosine monophosphate

COX = cyclooxygenase

GP = glycoprotein

TXA_2 = thromboxane A_2

RISK FACTORS FOR THROMBOEMBOLISM

Patient

· Age > 40 years
· Obesity
· Prolonged immobility (long plane trips, paralysis)
· Pregnancy / puerperium
· Oestrogen Rx (oral contraceptive)
· Previous DVT / PE
· FH DVT / PE
· Varicose veins
· Dehydration

Disease

· Fractures of pelvis, hip, lower limb
· Major surgery esp. abdominal / pelvic / orthopaedic involving lower limb
· Malignancy
· Heart failure
· Myocardial infarction (mural thrombus)
· Ventricular aneurysm
· Atrial fibrillation
· Infection e.g. pneumonia
· Inflammatory bowel disease
· Nephrotic syndrome
· Homocysteinaemia
· Paraproteinaemia (B cell neoplasms causing ↑↑gamma globulin levels)
· Polycythaemia (Erythrocytosis)
· Thrombocytosis
· ATT, Protein C, Protein S deficiencies
· Lupus anticoagulant (anti-phospholipid syndrome)
· Factor V Leiden (resistance to Protein C)
· Prothrombin gene mutation

Investigations for venous thromboembolism (VTE)

D-dimer

D-dimers are formed by the action of plasmin on cross-linked fibrin and imply the presence of a clot recently formed.

Elevated D-dimer levels may occur in the following situations:

◦ DVT

◦ Recent trauma

◦ Bleeding

◦ Hospitalisation

◦ Advanced age

◦ Malignancy.

This test is therefore not specific for deep vein thrombosis, but the diagnosis should not be considered if a negative result is obtained.

Doppler Ultrasound

This test is more reliable when deep vein thrombi are more proximally situated.

Pulmonary artery CT scan

This scan is helpful in locating an embolus in a major pulmonary artery, but may not detect more distally situated emboli

ECG

Sinus Tachycardia (one of the most common ECG findings in this situation)

T wave inversion V1 – V4 due to right ventricular strain (the commonest ECG abnormality in PE)

Ventricular ectopic beats

Atrial fibrillation

Right bundle branch block

SIQ3T3

S1 (Deep S wave in Standard Lead I) signifies development of acute right axis deviation due to sudden increase in right sided pressure and right ventricular dilatation.

Deep Q waves and T wave inversion develop in Standard Lead III - ? rationale for this

Echocardiography

Not performed routinely, but may show right ventricular hypokinesis, persistent pulmonary artery hypertension and free floating clot in right ventricle

Disseminated Intravascular Coagulation (DIC)

Widespread thrombus formation in small capillaries caused by:

1. Release of a substance into the circulation which initiates clotting

2. Widespread damage to endothelial cells → initiation of clotting

Thrombi (consisting of platelet aggregates plus fibrin) are laid down in small blood vessels → ischaemia and consumption of platelets and clotting factors → bleeding

Acute: bleeding predominates

Chronic: clotting predominates

Causes:
Release of a substance into the circulation which initiates clotting

·Sepsis	Endotoxins / exotoxins Monocytes release a procoagulant tissue factor
·Malignant neoplasms	Mucin Thromboplastin-like substance Procoagulant material in granules of malignant promyelocytes
·Obstetric related	Amniotic fluid Products of conception act as procoagulant material
·Head injury	Fat Phospholipids
·Massive tissue injury	Trauma Burns Surgery

Widespread damage to endothelial cells → initiation of clotting

Autoimmune
Meningococcaemia
Riccketsial infection
Severe infections

Miscellaneous

Snake bite – Taipan, Tiger, Brown and Red-bellied Black snakes
Shock
Heatstroke
Vasculitis
Aortic aneurysm
Liver disease

The laboratory investigation for DIC

The laboratory investigation should include:

- Coagulation tests aPTT, PT, thrombin time (TT)
- D-dimer
- Fibrin degradation products (FDP)
- Platelet count
- Haemoglobin
- Analysis of the blood smear.

These tests should be repeated over a period of 6–8 h because an initially mild abnormality can changed dramatically in patients with severe DIC.

Common findings include:

- Prolonged PT and/or aPTT
- Platelet counts ≤100 x 10^9/L, or a rapid ↓in platelet numbers
- Schistocytes (fragmented red cells) in the blood smear
- ↑FDP - the most sensitive test for DIC.

  (The diagnosis of DIC is unlikely in the presence of normal levels of FDP)
- ↑D-dimer. The D-dimer test is more specific for detection of fibrin (but not fibrinogen) degradation products and indicates that the cross-linked fibrin has been digested by plasmin.
- ↓Fibrinogen level

  Because fibrinogen has a prolonged half-life, plasma levels diminish acutely only in severe cases of DIC.
- ↓Antithrombin III & plasminogen levels may occur in high-grade DIC

Liver Function Tests and Lipids – learning objectives

Essential

Pre reading

- ✓ *Understand the 6 normal functions of the liver: digestive, metabolic, storage, excretion, haemopoiesis, phagocytosis*
- ✓ *Identify major anatomical features of the hepatobiliary system: lobes of liver, gall bladder, bile duct and CBD, portal and hepatic veins, hepatic artery*
- ✓ *Understand bilirubin metabolism: be able to draw the pathways showing metabolism of haem → bile etc*
- ✓ *Important acute phase proteins: ferritin, CRP*

In course

- ✓ Accurately interpret **Liver Function Tests** using clinical examples of viral hepatitis, obstructive jaundice and fatty liver:
- ➢ Bilirubin (unconjugated vs conjugated)
- ➢ Liver enzymes (GGT, Alk Phos, ALT, AST)

- ✓ Understand the **lipid pathways**: synthesis of the different lipoproteins (VLDL, LDL, HDL) and their functions as well as the key enzymes: lipoprotein lipase, hormone sensitive lipase, LCAT, HMG CoA reductase
- ✓ Understand the cause of **hyperlipidaemi**a in Type 2 diabetes
- ✓ Understand how urea and albumin levels can be used as a way of assessing liver function
- ✓ Be able to list the important secondary (possibly modifiable) causes of hyperlipidaemia: obesity, hypothyroidism, renal failure, alcohol excess.

- ✓ Other important enzymes: CK and LDH whose elevation may not be due primarily to hepatic pathology, such as:
  · LDH: (blood dyscrasias, metastases)
  · CK: (MI, CVA, myositis

Important

- ✓ List less common secondary (possibly modifiable) causes of hyperlipidaemia: nephrotic syndrome, drugs (thiazides, oestrogens, glucocorticoids), cholestatic jaundice.
- ✓ Understand other acute phase reactants: fibrinogen, prothrombin, haptoglobin, factor VIII, platelets, lipoprotein a, complement, caeruloplasmin

FUNCTIONS OF THE LIVER

1. Digestive

Production of bile to aid in digestion and absorption of fats and fat soluble vitamins

2. Metabolic

A most important organ in the metabolism of proteins, carbohydrates and fats.

3. Storage

Vitamin B12	sufficient stores for 1 – 3 years
Vitamin A	sufficient stores for 10 months
Vitamin D	sufficient stores for 3 – 4 months*
Vitamin K	stored in small amounts
Folic acid	stored in small amounts
Ferritin	apoferritin in hepatocytes binds with any excess iron to form ferritin. Iron is released from ferritin as required.

*children who live in cold climates and who remain indoors throughout the winter, may develop rickets in the springtime, as the stores of Vitamin D acquired during preceding summer have become exhausted.

4. Detoxification / excretion of drugs and other substances

e.g. steroid hormones, insulin, parathyroid hormone
thyroxine
calcium, copper
antibiotics, such as penicillin, erythromycin, sulfonamides

When liver disease is present, feminisation of the male can occur due to accumulation of oestradiol. This potent oestrogen is normally converted to the far less potent oestriol, when the liver is functioning normally.

5. Extra-medullary haemopoiesis

6. Phagocytosis

Kupffer cells lining the sinusoids phagocytose senescent red cells, bacteria and antigen:antibody complexes

Digestive function of the liver

Composition of Bile (600ml – 1L produced daily)

·**Bile salts** – manufactured from cholesterol, from which is derived cholic & deoxycholic acids. These combine with taurine & glycine, and finally sodium → bile salts.
·**Bilirubin**
·**Cholesterol, Fatty Acids, Lecithin**
·**Electrolytes**, such as calcium and copper.

Functions of Bile

1. Fat digestion and absorption
2. Excretion of bilirubin, cholesterol and other substances e.g. antibiotics

1. Fat digestion and absorption

Ingested fats, mainly triglycerides, are emulsified mainly in the small intestine together with bile. Lecithin is important in this emulsification process, and to a lesser extent, bile salts.In this process, the fat globules are transformed into very small particles, such that their surface area is ↑ 1000-fold, and this facilitates the action of pancreatic lipase to convert the TG → fatty acids and monoglycerides.
Bile salts now cover these molecules forming micelles, and transport them to the villi where they can be absorbed. In the intestinal cells, chylomicrons are formed and enter lymphatic channels→thoracic duct→blood stream.

2. Excretion

◦ **Cholesterol**
1 – 2 gm cholesterol is excreted / day in the bile.

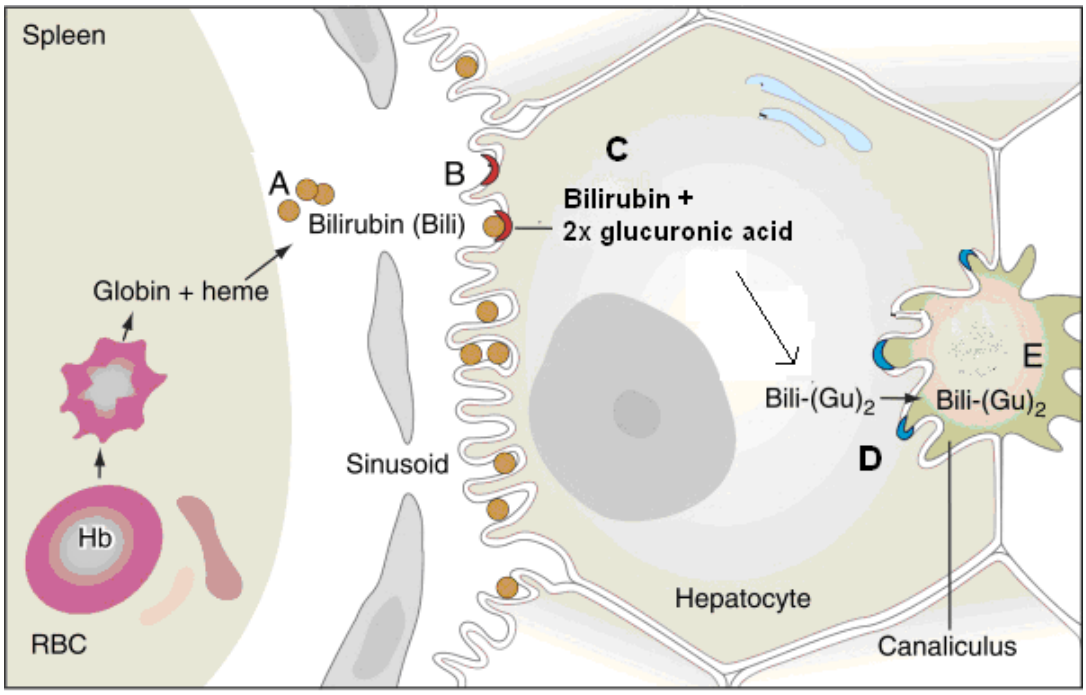
◦ **Bilirubin**

When the erythrocytes get old and frail after about 120 days in the circulation, they are phagocytosed by macrophages of the reticulo-endothelial system (RES), mainly in the spleen; their contained haemoglobin is broken down into iron and globin (recycled) and the remainder of the haem pyrrole ring is transformed into biliverdin and then to bilirubin. Bilirubin passes out of the spleen into the circulation where it binds to albumin, which carries it to the liver where it becomes conjugated in the hepatocytes to two molecules of glucuronic acid to form bilirubin diglucuronide.
This is excreted in the bile, passes to the intestine where it is converted to urobilinogen by intestinal bacteria. Of this, 20% is reabsorbed and a little (5%) appears in the urine as urobilinogen, and the remainder is re-excreted in the bile. In the urine, urobilinogen is oxidised to urobilin, which gives the urine its yellow colour.
The 80% urobilinogen which has not been absorbed into the portal blood, is reduced in the bowel to stercobilinogen. When this is oxidised to stercobilin, the faeces is given its brown colour, and indole, skatole, mercaptans and hydrogen sulphide are the malodorous products giving it its distinctive odour.

Van den Bergh Test:

Direct test is for conjugated bilirubin only
If methanol is added to the reaction, total bilirubin is measured (i.e. conjugated + unconjugated)
Indirect determination of the unconjugated form can then take place by subtraction of the two results.

Jaundice



Pathway of bilirubin transport and metabolism, from spleen to biliary canaliculus

A. Bilirubin is produced from metabolism of haem, primarily in the spleen, and is transported to the liver bound to albumin.

B. Bilirubin enters the hepatocyte by binding to a transporter protein (red crescents) and crosses the cell membrane thus entering the cell.

C. Bilirubin is then conjugated to glucuronic acid by the enzyme glucuronyl transferase producing bilirubin diglucuronide (Bili-$(Gu)_2$.)

D. This conjugated bilirubin is then actively secreted into the canaliculi

E. Once in the canaliculi, the conjugated bilirubin passes into the hepatic ducts and to the gall bladder or down the common bile duct with the other constituents of the bile.

*Bili = Bilirubin

Bili – $(Gu)_2$ = Bilirubin diglucuronide (conjugated bilirubin)

Haemolytic anaemia

In haemolytic anaemia, unconjugated bilirubin is produced at rates that exceed the ability of the liver to clear it, leading to an increase in unconjugated bilirubin in serum. (**A**)

Gilbert's disease

In Gilbert's disease, a genetically determined decrease in level of glucuronyl transferase results in build-up of unconjugated bilirubin in hepatocytes and ultimately in serum. (**C**)

In Gilbert's disease, there may also be a defect in the bilirubin transporter protein (B)

Neonatal jaundice

The level of glucuronyl transferase may be reduced in the neonate → neonatal jaundice.

Viral hepatitis

In hepatitis, jaundice is produced by three mechanisms:

1. The ability of the hepatocytes to conjugate bilirubin becomes impaired (**C**)
2. The active secretion of conjugated bilirubin into the canaliculi deteriorates (**D**)
3. Oedema may cause obstruction of the canaliculi → further cholestasis (**E**)

Thus these patients have ↑levels of both unconjugated and conjugated bilirubin in the blood.

Obstructive jaundice

In obstructive jaundice (which may be intra- or extra-hepatic) conjugated bilirubin is prevented from passing freely from the hepatocyte along its normal pathway to the duodenum (E) →↑levels of conjugated bilirubin in the blood.

There is a build-up of bile in the canaliculi, the back pressure eventually causing disruption of hepatocyte function and inability of the cells to process bilirubin derived from senescent red cells in the usual way (**C**). Eventually,↑levels of both unconjugated and conjugated bilirubin therefore occur in the blood.

Blood: ↑Bilirubin (conjugated and unconjugated)
↑ALP, GGT
↑Cholesterol*

Urine: +ve Bilirubin (conjugated therefore soluble in plasma and urine)**
-ve Urobilinogen (bilirubin not getting through to the small intestine due to obstruction)

Faeces: ↓stercobilin***

↓Absorption of fats including fat soluble vitamins (Vitamins ADEK)
→ Steatorrhoea
Osteomalacia
Bleeding tendency (↓Factors II, VII, IX, X)

*Xanthelasma, xanthomata
**Urine dark in colour
***Stools pale, fatty, floaty and foul-smelling

Metabolic Functions of the Liver

- **Proteins**
- **Lipids**
- **Glucose**

Protein Metabolism

1. Synthesis of non-essential amino acids by different processes, including transamination from keto-acids

e.g. aspartate from oxaloacetate

2. Catabolism of proteins to amino acids, which may then be further catabolised and enter the citric acid cycle with formation of urea, or be converted to glucose or fats.

Formation of urea:

$$NH_3 + NH_3 + CO_2 \rightarrow \begin{matrix} H_2N \\ \backslash \\ C = O \\ / \\ H_2N \end{matrix} + H_2O$$

Urea is formed from ammonia (NH3), this being a by-product of protein catabolism. In liver disease,

urea production ↓
and
ammonia builds up → hepatic encephalopathy

3. Manufacture of plasma proteins.

Albumin is manufactured at a rate of 12g/day. Albumin has a half-life of ~ 20 days, so a fall in albumin is a relatively *late* sign of liver disease.

Alpha & Beta Globulins (not Gamma Globulins – these being produced by B lymphocytes)

4. Production of clotting factors:

I, II, V, VII, VIII, IX, X, XI, XII (Von Willebrand factor is produced by endothelial cells)
Factor III is tissue thromboplastin; Factor IV is calcium; Factor VI does not exist.
Factor I (fibrinogen) ↑ in liver disease, but is often structurally imperfect and mal-functional. The production of the remainder of the clotting factors is impaired and because they have a short half-life, coagulation tests are abnormal within a *few days* of onset of liver disease.

5. Acute phase reactants (positive):

(These are produced mainly by the liver, in response to interleukin-6)

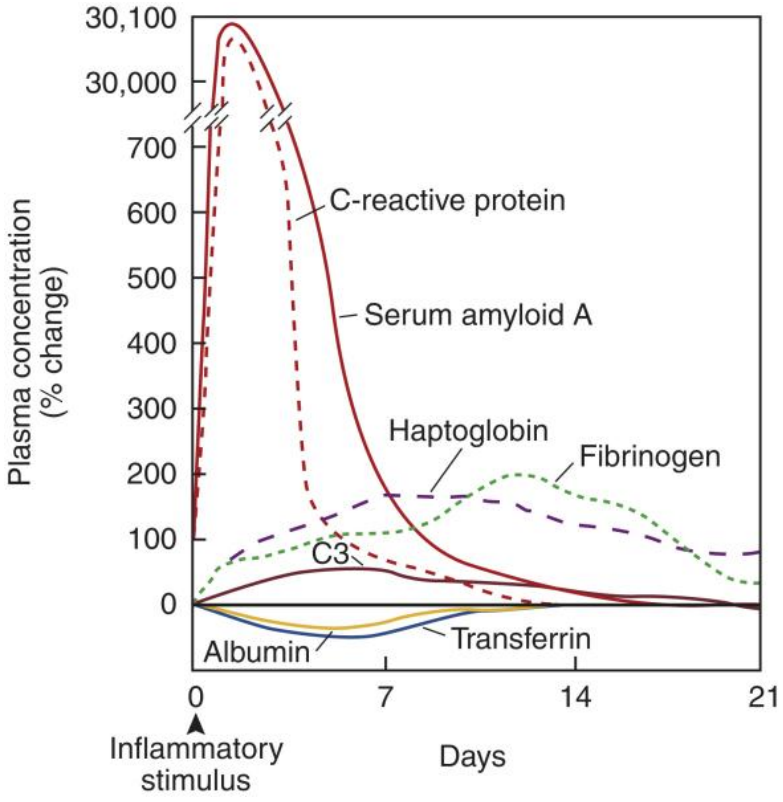
C-Reactive Protein (CRP)	Amyloid P and A
Caeruloplasmin	Haptoglobin
Ferritin	Mannose-binding protein
Alpha-1 Antitrypsin	Complement
Fibrinogen	Plasminogen activator inhibitor
Prothrombin	Lipoprotein (a)
Factor VIII	Hepcidin
*von Willebrand factor	
*Platelets	

* von Willebrand factor produced by endothelial cells
* Platelets produced in bone marrow
* thrombogenic

CRP is commonly measured as it parallels the severity of inflammation / infection / tissue injury, and may be used as a marker for recovery / response to Rx

Acute phase reactants (negative):

Albumin
Transferrin



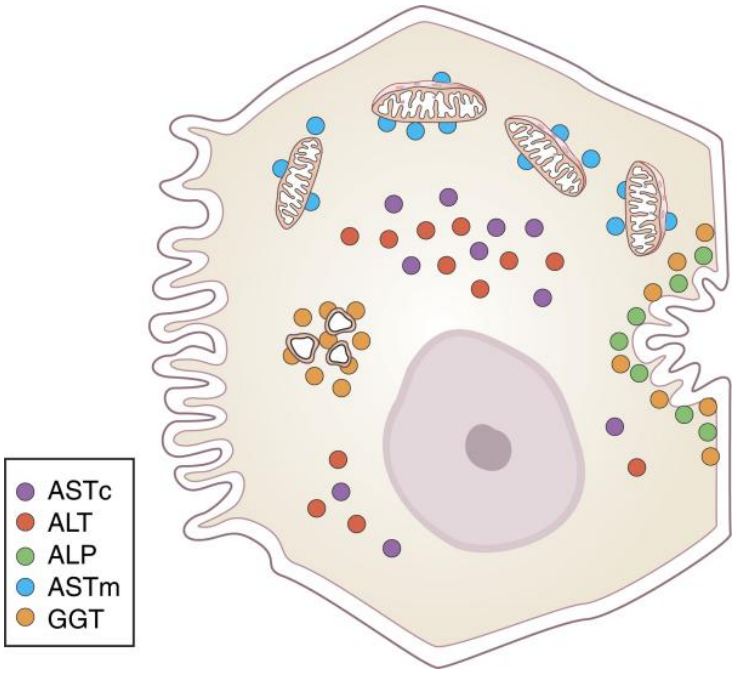
Typical plasma acute-phase protein changes after a moderate inflammatory stimulus. Several patterns of response are seen: major acute-phase protein, increase 100-fold (e.g., C-reactive protein and serum amyloid A); moderate acute-phase protein, increase 2-fold to 4-fold (e.g., fibrinogen, haptoglobin); minor acute-phase protein, increase 50% to 100% (e.g., complement C3); and negative acute-phase protein, decrease (e.g., albumin, transferrin)

6. Enzymes produced in the liver

*Alanine aminotransferase	ALT
*Aspartate aminotransferase	AST
*Alkaline phosphatase	ALP / Alk. Phos.
*Gamma glutamyl transferase	GGT / Gamma GT
Lactate dehydrogenase	LDH
Creatine kinase	CK
Alpha-1 anti-trypsin	AAT

* Used routinely as part of the assessment of liver function

Location of hepatocellular enzymes



Alanine aminotransferase (ALT) and the cytoplasmic isoenzyme of aspartate aminotransferase (ASTc) are found primarily in the cytosol. With membrane injury as in viral or chemically-induced hepatitis, these enzymes are released and enter the sinusoids, raising plasma AST and ALT activities. Mitochondrial aspartate aminotransferase (ASTm) is released primarily with mitochondrial injury, as caused by ethanol as in alcoholic hepatitis. Alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) are found primarily on the canalicular surface of the hepatocyte. Bile acids accumulate in cholestasis and dissolve membrane fragments, releasing bound enzymes into plasma. GGT is also found in the microsomes, represented as rings in the figure; microsomal enzyme-inducing drugs, like phenobarbital and dilantin, can also increase GGT synthesis and raise plasma GGT activity.

TRANSAMINASES **(syn: Transferases)**

ALT	**Alanine**	**Aminotransferase**
AST	**Aspartate**	**Aminotransferase**

Two isoforms of AST: **ASTc (cytosolic AST)**
ASTm (mitochondrial AST)

Half-lives of transferases

ALT 47 hours
ASTc 17 hours
ASTm 87 hours

Location & specificity of transferases

ALT
ALT is found in the cytoplasm of the hepatocytes, where it is present in much lower amounts than is ASTc.
Initially, when the hepatocyte is damaged and the transaminases are liberated into the bloodstream, the ASTc level in the blood is much higher than is the ALT level, but because of the shorter half-life of AST, the level falls faster than does ALT. Thus, if the blood levels of these two enzymes are measured some time after the hepatocyte injury, the ratio of AST:ALT will be found to be < 1.

ALT is sensitive to liver cell injury & is more specific for liver disease than is AST, which is ubiquitous in the cells of the body, although present in greatest amounts in hepatocytes.

The only other organ in which ALT is found is the kidney. Its level in the blood rarely rises in conditions affecting the kidney.

AST
AST is present in the cytoplasm of the hepatocyte (ASTc) as well as in the hepatic mitochondria (ASTm)

Found in:	***Increased in:***	***Decreased in:***
Liver	liver disease → hepatocyte damage	
Heart	MI	
Brain	NS disease e.g. CVA	
Skeletal muscle	muscle injury	
Kidney		Chronic renal failure

Elevation in the AST:ALT ratio

If ratio of AST:ALT changes to >2 with a concomitant ↑GGT, this is suggestive of alcohol-induced liver disease; a ratio >3 is highly suggestive.

The elevation in the ratio is caused by:

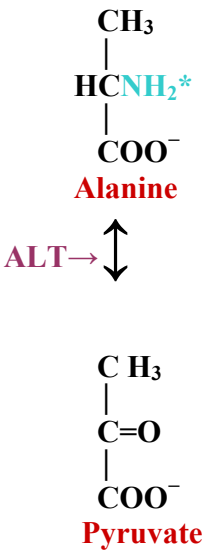
· Alcohol-induced mitochondrial damage → release of ASTm (in addition to the release of cytosolic AST and ALT)
· Vitamin B6 (pyridoxine) deficiency in alcoholism → ↓levels of ALT & AST
Both ALT and AST depend on Vitamin B6 for their activity, ALT being more dependent than AST in this regard.

Function of transferases

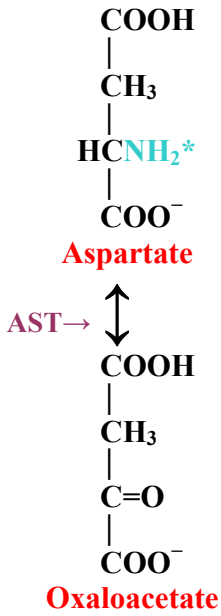
The aminotransferase enzymes transfer (reversibly) an amino group from an amino radical donor, such as *glutamine*, to a *ketoacid* to form an amino acid

e.g. amino group transferred to pyruvate, to form alanine
amino group transferred to oxaloacetate to form aspartate.

Transamination of pyruvate to form alanine



Transamination of oxaloacetate to form aspartate



***amino group**

ALKALINE PHOSPHATASE (ALP)

A group of isoenzymes which hydrolyse phosphate ester bonds in an alkaline medium, (ideally PH 9.0) generating an organic radical + inorganic phosphate

Found in:	***Increased in:***
Liver	•Hepatocellular damage •Cholestasis •Metastatic disease of the liver •Passive congestion *Levels*: ++++ in metastatic liver disease (prod by tumour & → obstruction) +++ in cholestasis ++ in hepatitis
Bone	ALP inactivates pyrophosphate, which is an inhibitor of mineralisation of osteoid. The level of ALP ↑ in any cause of ↑ bone turnover, such as: •Paget's disease of bone •Metastatic bone disease •Physiologically at the extremes of life; Children especially < 2 yrs Teenagers at times of rapid growth The elderly commonly 1.5x normal level •Osteomalacia & rickets •Hyperparathyroidism
Placenta and Lactating breast	•In pregnancy may reach 2 – 4 x normal by term
Wall of small intestine	•After a high fat meal (digestion of ingested phospholipids)
Tumours e.g.:	•Ca Lung •Hypernephroma ▫Hodgkin disease

If *Gamma GT* is not ↑ along with the ALP, the ALP may be originating from a site other than the liver, e.g. bone. ALP resides near the biliary canaliculi, in the hepatocyte cell membrane.

GAMMA GLUTAMYL TRANSFERASE (Gamma GT, GGT)

- Transfers a gamma glutamyl group from glutathione to amino acids, which enables them to be transported across cell membranes.
- GGT is involved in the regeneration of active glutathione (gamma glutamyl-cysteinyl-glycine), thus maintaining adequate levels of this important antioxidant.

The enzyme is found in the epithelial cells of the bile ducts and inside the microsomes of hepatocytes.

Found in:	***Increased in:***
Liver	•liver disease, esp cholestasis •↑enzyme synthesis induced by: ◦alcohol excess* ◦drugs e.g. anti-TB anti-epileptic paracetamol

*↑GGT in 60 – 70% alcoholics; level may remain ↑ for up to 1/12 after onset of abstinence

Pancreas

Kidney

GGT level in blood does not ↑ in these pancreatic and renal conditions, but ↑ levels may be present
- in the pancreatic secretions
- in the urine (GGT resides in the brush border of tubular cells)
  e.g. Nephrotoxic drugs such as Cisplatin

*****

Functions of Glutathione

1. Antioxidant

Glutathione is found in many cells throughout the body and plays an important role in converting toxic hydrogen peroxide to water.

GSH = active glutathione
GS = inactive glutathione

$$\text{GSH} \xrightarrow{\text{GGT}} \text{GS} + \text{H}^+ \rightarrow \text{GS} \rightarrow \text{GSH}$$

$$\downarrow$$

$$\text{H}_2\text{O}_2 + 2\text{H}^+ \rightarrow 2\text{H}_2\text{O}$$

2. Metabolism and Excretion of drugs

Glutathione forms complexes with certain drugs, enabling them to be excreted
e.g. paracetamol, phenytoin, carbemazepine

3. Amino acid transport across cell membranes

Elevated Liver Enzymes

↑Transaminases (ALT usually >AST)

Caused by damage to hepatocytes. These enzymes are present in the cytoplasm of the hepatocytes and are therefore readily released into the circulation when the integrity of the cell is disrupted.

Causes of hepatocyte damage

- **Viral infections**
- **Toxic substances**
- **Hypoxia**
- **Non-alcoholic fatty liver (NAFL)**

Viral infections
- Hepatitis A, B, C, D, E
- Epstein-Barr virus (EBV)
- Cytomegalovirus (CMV)
- Herpes Simplex virus

Toxic substances
- Alcohol
- Drugs e.g. Paracetamol, NSAIDS, statins, chemotherapy drugs, Amiodarone
- Copper Wilson's disease

Hypoxia
Any cause of ↓perfusion of the liver→ hypoxic damage to the hepatocytes such as:
- Acute LV failure e.g. Acute MI
- Septic shock endo- and exotoxins and cytokines → hypotension

Non-alcoholic fatty liver (NAFL)
Accumulation of triglycerides inside hepatocytes in the obese patient; the enzyme elevation is reversible with weight loss

↑Transaminases (AST > ALT)

- Alcohol damages mitochondria where mitochondrial AST resides (ASTm) as well as damaging the hepatocyte membrane causing leakage of cytosolic AST (ASTc) into the circulation. Hence disproportionate ↑AST compared to ALT, which is only found in the cytoplasm.
- Fulminant hepatic failure (viral hepatitis)
- Reye's syndrome (severe illness with liver failure and depressed level of consciousness in children with a viral infection, often occurring after aspirin use)

↑Alkaline Phosphatase and Gamma GT (simultaneous elevation of both enzymes)

Caused by biliary tract obstruction
- **Extra-hepatic**
- **Intra-hepatic**

Extra-hepatic Obstruction

Common Causes
- Gallstones
- Carcinoma head of pancreas

Less Common Causes
- Pancreatitis/pancreatic pseudocyst
- Stricture of common bile duct

Intra-hepatic Obstruction

Causes
- Hepatitis
- Drugs
- Primary biliary cirrhosis
- Liver metastases

In **viral hepatitis**, oedema due to inflammation results in obstruction of tiny intra-hepatic biliary canaliculi; there is also a failure of secretion of bile into the canaliculi by the hepatocytes, as the cell is metabolising too poorly to perform this energy requiring function.
The bile accumulates in the cell and the bile salts start to digest the cell membrane wherein these enzymes are situated (at site of exit of canaliculi from the cell), thus releasing the alkaline phosphatase and gamma GT enzymes into the cytoplasm and then into the circulation, as the integrity of the whole cell is disturbed.

>45 **Drugs** have been implicated in cholestatic jaundice – the agent causes acute hepatitis which is followed by chronic damage to the intra-hepatic biliary system.
Some examples:
Flucloxacillin, Erythromycin, Tetracycline, Chlorpromazine, Ibuprofen, oestrogens, Captopril (ACE inhibitor), anabolic steroids

Primary biliary cirrhosis – possibly an autoimmune condition affecting middle-aged females → inflammation commences in portal tracts and spreads to lobules, eventually → fibrosis and distortion of architecture (cirrhosis); biliary canaliculi become non-patent.

Liver metastases as they enlarge → compression of biliary canaliculi with obstruction

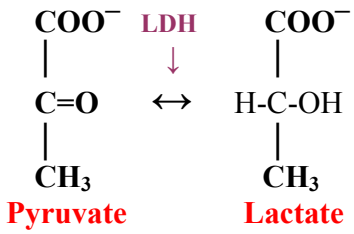
↑Gamma GT (disproportionate ↑GGT compared to the other liver enzyme levels)

Caused by enzyme induction by alcohol or drugs, such as Isoniazid, Phenytoin – these agents stimulate hepatocytes to produce Gamma GT (important in metabolism of glutathione, which is required to metabolise the substance)

LACTATE DEHYDROGENASE (LDH)

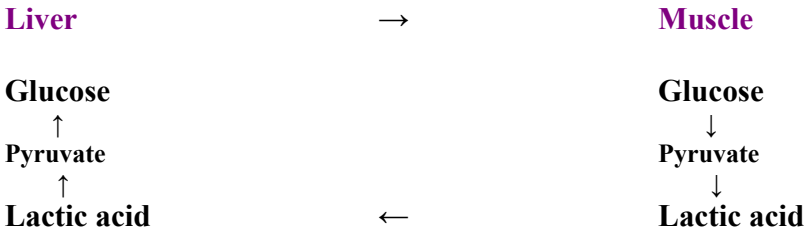
Present in:	*Increased in:*
Blood cells	Haemolysis, haematological malignancies
Heart	Myocardial damage eg MI
Lung	Pulmonary embolism
Brain	Seizures, cerebral damage, CVA
Skeletal muscle	Trauma involving skeletal muscle
Kidney	Renal disease
Liver	Hepatitis, 1° or 2° hepatic malignancy*
Pancreas	Pancreatitis
Placenta	Hypotension / shock
	Malignancies other than haematological e.g. metastatic melanoma

*LDH produced by tumour &/or released from hepatocytes



Cori cycle

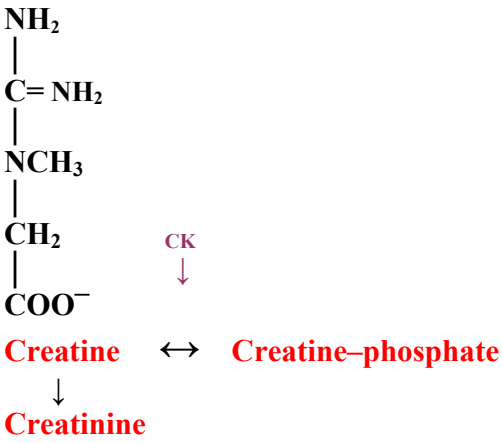
Lactic acid accumulates from glucose metabolism in working muscle, travels to the liver, where it is converted back to glucose, which then can replenish the glucose level in the myocytes.



CREATINE KINASE (CK) Three isoenzymes: **CK-MM, CK-BB, CK-MB**

Found in:		***Increased in:***
Skeletal muscle	CK-MM (98%) & CK-MB (2%)	myositis, muscle damage
Myocardium	CK-MM (70%) & CK-MB (30%)	MI
Brain, lung & other tissues	CK-BB	CVA, PE, hypothyroidism, DM

Creatine is formed in the liver from the amino acids, arginine, glycine and methionine; it is then transported to skeletal muscle, where CK catalyses its conversion → Creatine-PO4, which serves as an energy store for the muscle. CK also catalyses the reverse reaction, whereby ATP is released.



Causes of Hepatic Cirrhosis

Most common causes

Alcoholism	60 – 70%
Chronic viral hepatitis (B & C)	10%

Less common causes

NASH (non-alcoholic steato-hepatitis)
Haemochromatosis
Chronic obstructive jaundice
Right-sided heart failure
Drug-induced e.g. Methyldopa
Syphilis
Wilson's disease
Alpha-1 antitrypsin deficiency
Cystic fibrosis
Cryptogenic

Chronic viral hepatitis

Chronic hepatitis C most common in western world, chronic hepatitis B more common in Asia & Africa

Chronic obstructive jaundice

Primary biliary cirrhosis	Middle-aged ♀, cause unknown, AMA +ve in 90%
Primary sclerosing cholangitis	Associated in many patients with ulcerative colitis; cause unknown, P-ANCA +ve in 65%
Secondary biliary cirrhosis	e.g. bile duct stricture

Cryptogenic

Cause cannot be identified. (biopsy in established, endstage cirrhosis non-diagnostic)

Hepatic syndromes in the critically ill patient

Two hepatic syndromes occur in the critically ill patient:

1. Ischaemic hepatitis — secondary to hypoxia
2. Intra-hepatic cholestasis — secondary to inflammation

1. Ischaemic hepatitis

This occurs secondary to hypoxia. The hepatocytes release massive amounts of transaminases followed by a moderate increase in bilirubin (< 100 µmol/L). This is often accompanied by prolongation of the PT and PTT, and lactic acidosis, due to impaired hepatic function. (↓production of clotting factors, ↓absorption of vitamin K, ↓ conversion of lactate back to pyruvate)

These patients usually recover fully if they survive (akin to acute tubular necrosis in the kidney)

2. Intra-hepatic cholestasis

This occurs secondary to an inflammatory response to trauma or sepsis. Bile fails to be secreted into biliary canaliculi → accumulation of bilirubin inside hepatocytes (mainly conjugated bilirubin)

Six fundamental patterns of liver function tests

Condition	AST	ALT	ALP	Albumin	Bilirubin	Ammonia
Hepatitis	↑↑	↑↑	↑	**N**	↑↑	**N**
Cirrhosis	**N**	**N**	**N/sl↑**	↓	**sl↑**	↑
Biliary obstruction	↑	↑	↑↑	**N**	↑↑	**N**
***Space-occupying lesion**	**N/↑**	**N/↑**	↑	**N**	**N/↑**	**N**
Passive congestion	**sl↑**	**sl↑**	**N/sl↑**	**N**	**N/sl↑**	**N**
Fulminant liver failure	↑↑↑	↑↑	↑↑	↓	↑↑	↑

*often ↑LDH as well

Nonalcoholic Fatty Liver (NAFL)

This common condition is caused by an accumulation of lipid (mainly triglyceride) inside hepatocytes, and is manifest by ↑level of transaminases (2 -3 x normal levels). There seems to be a low risk of progression to cirrhosis.

Some individuals have an inflammatory infiltrate and progression to hepatocyte destruction, and these may account for some cases of "cryptogenic cirrhosis".
This sub-group of NAFL is known as NASH (non-alcoholic steatohepatitis).

Aetiology

- 97% Obesity
- 3 % · Type II Diabetes with its attendant dyslipidaemia
  · Hyperlipidaemia due to a cause other than diabetes
  · Drugs e.g. Corticosteroids, Oestrogens, Tamoxifen

Symptoms and signs

Most patients are asymptomatic. They may have hepatomegaly.
Some may experience fatigue or RUQ pain.
Those who progress to cirrhosis may develop symptoms of chronic liver disease.

Treatment

Weight loss is required in the vast majority of patients.

Acute fatty liver of pregnancy is a different entity, occurring in the latter part of pregnancy or the puerperium. Thought to be due to an abnormality in lipid metabolism, resulting in deposition of lipid in the maternal liver. These patients become extremely ill, with anorexia, jaundice, and DIC. They have been found to have low levels of Anti-thrombin III.
Treatment consists of transfusion of FFP and prompt delivery of the foetus.

Haemochromatosis

Haemochromatosis is a common disorder of iron storage in which an inappropriate increase in intestinal iron absorption results in deposition of excessive amounts of iron in parenchymal cells with eventual tissue damage and impaired function of organs.

The disease is caused by inheritance of a mutant gene, termed HFE. The condition can be recognised early on before organ damage has occurred. (genetic testing of first degree relatives, iron studies) Haemochromatosis implies potentially severe progressive iron overload leading to fibrosis and organ failure. Cirrhosis of the liver, diabetes mellitus, arthritis, cardiomyopathy, and hypogonadotrophic hypogonadism are common manifestations.

Haemochromatosis is one of the most common genetic diseases. It is most common in populations of northern European extraction in whom approximately 1 in 10 persons are heterozygous carriers and 0.5% are homozygotes.

Expression of the disease is modified by several factors, especially alcohol consumption and dietary iron intake, blood loss associated with menstruation and pregnancy, and blood donation. The disease is 5 to 10 times more frequent in men than in women.

Nearly 70% of affected patients develop the first symptoms between ages 40 and 60. The disease is rarely evident before age 20, although with family screening and periodic health examinations, asymptomatic subjects with iron overload can be identified, including young menstruating women. The penetrance of the mutation is variable. Thus, 30% or more of homozygous individuals do not have evidence of iron overload.

There is an increased incidence (14%) of hepatocellular carcinoma in males with long-standing haemochromatosis.

Laboratory Findings in Hereditary Haemochromatosis

Iron Studies	
Serum iron level	High normal /↑
Serum transferrin level	Normal
% Saturation	↑↑
Serum ferritin level	Markedly ↑
Liver Biopsy	
Hepatic iron concentration	Markedly ↑
Total Body Iron*	Markedly ↑ (≤ 50g)

***Normal values**

Male	3.5g
Female	2.5g

Suspected Liver Disease

↓blood taken for LFT

Abnormal liver function tests

↓ **Hepatitic:** ↑↑ **ALT** ↑↑ **AST** ± ↑ **ALP/GGT**	↓ **Cholestatic**: ↑↑ **ALP** ↑↑ **GGT** ↑ **ALT / AST**
↓ **Diagnostic Evaluation** Drug and alcohol history 1. Hepatitis screen 2. Auto-antibody screen: - ANA - SMA 3. EBV 4. Caeruloplasmin 5. α-1-AntiTrypsin 6. Ferritin 7. α-Fetoprotein	↓ **Diagnostic Evaluation** Drug and alcohol history 1.Auto-antibody screen: - AMA - ANCA 2.Imaging studies – CT / US / MRI / ERCP

*ANA = Anti-nuclear antibody
*SMA = Smooth muscle antibody
*EBV = Ebstein Barr Virus
*AMA = Anti-mitochondrial Antibody
*ANCA = Anti-neutrophil cytoplasmic Ab

ANA, SMA +ve in autoimmune diseases such as SLE
AMA +ve in Primary Biliary Cirrhosis
ANCA +ve in Primary Sclerosing Cholangitis

LIPIDS

Lipids are water insoluble organic hydrophobic molecules.
Found in cell membranes, and within cells where they form borders between various aqueous compartments, lipoproteins and adipocytes and take part in the synthesis of many compounds, such as vitamins and hormones.
We ingest 60 – 150gm lipids/day, mostly in the form of triglycerides (TG) - 90%;
10% as cholesterol, cholesterol esters, unesterified "free" fatty acids, phospholipids

Functions of lipids

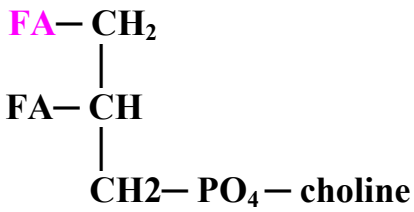
Fatty acids

- •Energy source
- •Insulation
- •Omega-3 fatty acids →↓VLDL blood levels by enhancing the action of lipoprotein lipase and promoting β-oxidation of FA
- •Substrate for gluconeogenesis (glycerol from triglycerides)
- •Form esters with cholesterol so that HDL can take up the esterified cho;esterol

Phospholipids Made up of **FA + phosphoric acid + nitrogenous base**

3 Types of phospholipid:
Cephalin
Lecithin
Sphingomyelin

Structure of Lecithin (phosphatidyl choline)



- •Constituent of lipoproteins, therefore important in transport of lipids
- •Donates an acyl group (**FA**) for the esterification of cholesterol, thus enabling it to be taken up by HDL

Cholesterol + **FA** → **Cholesterol** - **FA**
Free cholesterol **Cholesterol Ester**

- •Phosphate donor in metabolic reactions
- •Form part of structure of cell membranes
- •Myelin sheath around nerve fibers – acts as electrical insulator
- •Thromboplastin -- initiates clotting cascade
- •Prostaglandin production
- •Emulsification of fats in the small intestine
- •Constituent of surfactant

Cholesterol

Cholesterol occurs in the *exogenous* form (ingested) and the *endogenous* form (manufactured by many tissues, especially the liver, also adrenal cortex, ovary, testis and intestine). On a normal diet, our endogenous production of cholesterol > exogenous supply.

The process of endogenous production of cholesterol begins with the combination of several molecules of Acetyl CoA, resulting in formation of Hydroxy-methyl-glutaryl-CoA. HMG-CoA reductase catalyses the conversion to Mevalonic acid. The statin group of drugs act here to competitively inhibit this enzyme.

Ultimately, cholesterol results with its steroid structure of 4 fused hydrocarbon rings and attached 8-carbon side chain.
The steroid ring structure of cholesterol cannot be metabolised, therefore it must be excreted by conversion to bile salts or secreted in the bile.

- Forms a part of cell membranes
- Converted to bile acids (80% cholesterol is converted to bile acid)
- Production of hormones – cortisol, aldosterone, oestrogen, progesterone, testosterone
- Deposited in the stratum corneum of our skin and prevents excessive fluid loss by sweating. Severely burned patients can lose liters of fluid due to loss of this protective layer.
- Substrate for vitamin D production in the skin.

Fat Metabolism

1. Manufacture of cholesterol
2. Esterification of cholesterol to form:
3. Manufacture of fatty acids (FA) and triglycerides if there is an excess of amino acids and glucose
4. Catabolism of FA to CO_2 (β-oxidation of fatty acids) for energy
5. Production of ketone bodies from Acetyl-CoA
6. Gluconeogenesis from glycerol released by breakdown of triglycerides.

Fatty Acid Synthesis

When there is a state of excess glucose and protein, (when we take in more than we require), fatty acids are synthesized from acetyl CoA, which is the end product of metabolism of proteins, carbohydrates and fats. Acetyl CoA is carboxylated to Malonyl CoA and these two form the building blocks for FA synthesis. Ultimately, 3 x FA combine with glycerol → TG, which is the form in which the fat is stored.

Fatty Acid Catabolism

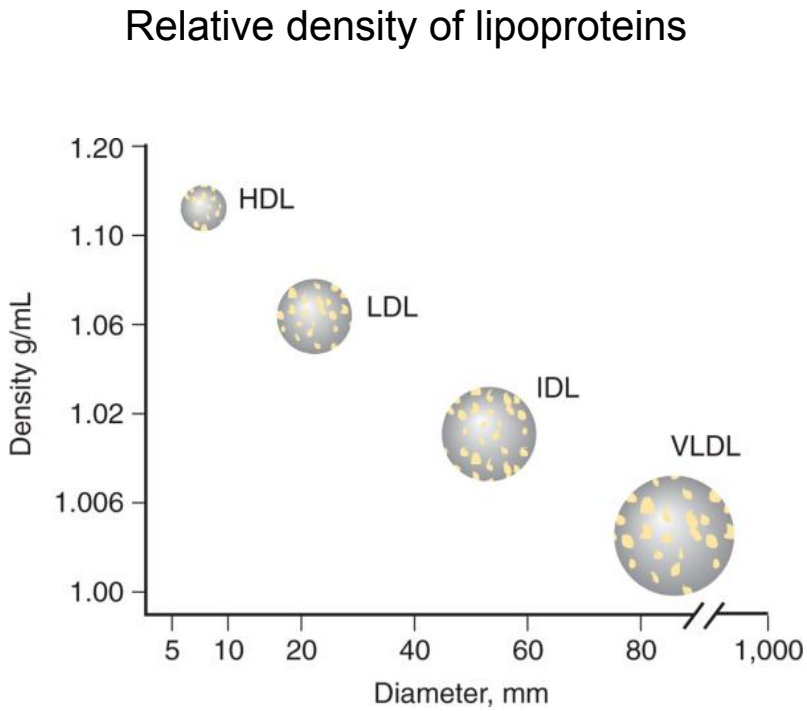
Conversely, *when our intake in insufficient for our metabolic needs*, TG are broken down in adipose cells → FA and glycerol, the FA traveling to tissues to supply them with energy, and FA plus glycerol traveling to the liver. Here, glycerol enters the pathway for glucose metabolism and FA are catabolised → Acetyl CoA.

The accumulation of acetyl CoA inhibits the enzyme responsible for formation of citrate from oxaloacetate and promotes entrance of oxaloacetate into the pathway for gluconeogenesis.
Thus, the Acetyl CoA is prevented from entering the Citric Acid Cycle, and instead is converted → acetoacetate (ketone body); the ketone bodies then leave the liver to provide energy to the tissues, especially the brain, which is not able to use FA for energy, as they do not cross the Blood Brain Barrier.

Lipoproteins

- Types of lipoproteins
- Functions of lipoproteins
- Enzymes involved in lipoprotein life cycle
- Lifecycle of lipoproteins
- Fasting Lipid Screen

Types of Lipoproteins



The density of the several classes of lipoprotein is inversely proportional to the ratio of lipid, particularly triglyceride, to protein. As lipid is less dense than protein, the more lipid contained in the particle increases its size and decreases its density. HDL, high-density lipoprotein; LDL, low-density lipoprotein; IDL, intermediate density lipoprotein; VLDL, very low density lipoprotein.

VLDL is synthesised in the liver.
LDL is derived directly from VLDL. As TG is off-loaded from VLDL (to form IDL), and cholesterol is then acquired from HDL, IDL then becomes LDL

TG
↑
VLDL → LDL
↑
Cholesterol

HDL is synthesised de novo in the liver (main site of production) and also in the GIT.

Functions of Lipoproteins

VLDL transports TG from the liver (where they are assembled) to adipose tissue for storage.
LDL transports cholesterol to the various tissues which require it e.g. skin for Vitamin D synthesis.
HDL

- Provides proteins to VLDL and chylomicrons from its protein layer, so that lipoprotein lipase (LPL) may recognise them.
- Exchanges fats with the VLDL remnant, thus converting it to LDL
- Mops up any cholesterol not required by tissues and possibly also that which is being deposited at sites of endothelial damage.

Enzymes

Lipoprotein lipase – breaks down TG inside chylomicrons and VLDL, liberating FFA
Hormone sensitive lipase - breaks down TG inside adipose tissue, liberating FFA
LCAT – Esterifies cholesterol with a FA derived from lecithin, thus enabling HDL to take up the cholesterol.

Lifecycle of lipoproteins

Cholesterol and triglycerides (TG) are insoluble in water, so must be transported in plasma as lipoproteins, the inner core of hydrophobic cholesterol and TG being surrounded by a shell of amphiphobic phospholipid and hydrophilic protein.

The more triglyceride the lipoprotein carries, the lower its density. Chylomicrons are the least dense of the lipoproteins.

Chylomicrons are formed in the intestinal cells from dietary sources of triglycerides, cholesterol, phospholipids and protein. They enter the thoracic duct and thence the blood, where they interact with HDL. Proteins are received from HDL, including apo C II, which makes the chylomicron functional, in that lipoprotein lipase is now able to break down the triglycerides contained inside the chylomicron and liberate FA. These enter the adipose cells where they are stored and muscle cells where they provide energy. Any FA not immediately taken up by cells becomes bound to albumin. Glycerol travels to the liver where it is used in TG synthesis or enters the glycolytic pathway.

The chylomicron, which by now has lost most of its TG, interacts again with HDL, giving back the borrowed protein and the remnant travels to the liver where it is degraded into its component parts.

VLDL are formed in the liver and their function is to carry TG to the tissues. The VLDL reacts with HDL, receiving the necessary protein to make it functional; lipoprotein lipase breaks down the TG releasing glycerol and FA as with the chylomicrons.

The VLDL now reacts again with HDL, returning the borrowed protein and receiving cholesterol, becoming cholesterol-rich LDL. At the same time, any remaining TG is donated to the HDL which returns it to the liver.

The LDL are endocytosed by tissue cells and their contained cholesterol is liberated for use by the cell. If cholesterol is not required, the LDL takes it back to the liver for excretion.

HDL is formed by the liver and intestine as a disc shaped particle consisting of apoprotein and phospholipid. The HDL particles travel to the tissues where they soon become spherical as they avidly collect cholesterol from tissues and from IDL. The free cholesterol is esterified with an acyl group from the phospholipid, phosphatidylcholine, under the influence of LCAT* also known as PCAT**. Cholesterol is transported as an ester; it cannot be incorporated into HDL unless it is esterified by LCAT. The HDL then returns to the liver and offloads its cargo of cholesterol, which is destined for excretion in the bile. So HDL acts like a mop, cleaning up the cholesterol before it can be deposited on the vessel walls to form an atheromatous plaque.

In liver disease, cholesterol levels are often ↓ due to decreased de novo synthesis of cholesterol and apoprotein, (↓lipoprotein formation) whereas in cholestasis, levels of *free* cholesterol ↑ due to ↓production of LCAT→↓formation of cholesterol esters from phospholipids. When this is the case, the lipid-poor HDL are catabolised at an ↑rate → ↓ levels of HDL.
Also, when there is obstruction to bile flow → cholesterol cannot be excreted in the bile in the usual way.

* LCAT = lecithin:cholesterol acyl transferase
**PCAT = phosphatidylcholine acyl transferase

(LCAT and PCAT are synonyms, lecithin being a synonym for phosphatidylcholine)

Fasting Lipid Screen

The fasting state is required so that the chylomicrons will have been cleared from the circulation. (This occurs 2 – 10 hours post-prandially). As the chylomicrons transport large amounts of lipid from the GIT (especially TG), the lipid screen assessed in the non-fasting state is not a true reflection of the lipid content of the other lipoproteins, particularly VLDL, which mainly carries TG.

Total cholesterol value is obtained by measuring the cholesterol which is carried mainly in HDL and LDL. (a small amount in VLDL).

HDL-cholesterol can be measured directly, and LDL-cholesterol is then derived according to the Friedewald formula:

$$\textbf{LDL-Cholesterol} = \{(\textbf{Total Cholesterol} - \textbf{HDL-Cholesterol}) - \textbf{TG*}\} \div \mathbf{2.19}$$

*only valid if TG <4.5 mmol/l

Total TG value largely reflects the TG carried in VLDL. A very small amount is present in HDL.

Aetiology of Hyperlipidaemia

1. Primary (Familial)
2. Secondary to: **Obesity/high fat diet**
Nephrotic Syndrome
Chronic Renal Failure
Alcohol excess
Chronic Cholestatic Jaundice
Hepatitis
Drugs **e.g. beta blockers, thiazides, oestrogen, corticosteroids**
Endocrinopathies
- **Hypothyroidism**
- **Hypopituitarism**
- **Diabetes Mellitus**
- **Cushing's syndrome**

High risk lifestyle

Obesity/ ↑fat diet

High intake of carbohydrates and fats
e.g. Fat intake constitutes >40% of total calorie intake
Saturated fats >10% of total calorie intake.

Saturated fatty acids inhibit hepatic LDL receptors →↑circulation time of LDL; they also appear to promote formation of cholesterol from Acetyl CoA
Cholesterol >300mg/day

Consumption of excessive amounts of carbohydrates → ↑↑Acetyl CoA which is converted to triglycerides and transported out of the liver in VLDL.
↑Adipose tissue mass acts as an endocrine organ, releasing FFA and cytokines. FFA travel to the liver, where they are incorporated into VLDL →↑VLDL levels. FFA & cytokines promote insulin resistance → ↓lipoprotein lipase function →↑circulation time of VLDL. and ↓HDL synthesis.

Nephrotic Syndrome

Hepatic lipoprotein synthesis is stimulated as a response to the low oncotic pressure of the ECF. This → ↑VLDL and ↑LDL. In this situation, LDL are synthesized de novo in the liver. There is also ↑hepatic synthesis of cholesterol.
↓LCAT→ ↑free cholesterol
↑Lp(a)

Chronic Renal Failure

↑CRP levels
Insulin resistance → ↑VLDL
↑Production of Lipoprotein a
↑Production of homocysteine
↑Oxidised LDL levels

Alcohol excess

Impairment of function of lipoprotein lipase thus preventing triglycerides in VLDL from being broken down to FFA and entering adipocytes→ ↑circulation time of VLDL
↓β-Oxidation of FFA in the liver, so ↑incorporation of FFA into VLDL

Hepatitis

↑VLDL production

Cholestatic Jaundice

↑Free cholesterol and ↓HDL
·↓Formation of LCAT (→ cholesterol esterification inhibited and ↓uptake of cholesterol into HDL→↑free cholesterol levels)
·↓Excretion of cholesterol in bile.
·↓HDL due to↑rate of breakdown of cholesterol-poor HDL

Diabetes Mellitus

·↓Function of lipoprotein lipase ↑circulation time of VLDL
·↑Function of hormone sensitive lipase inside adipoctyes → breakdown of TG and FFA release into circulation
·Glycosylation of lipoproteins causes impairment of their metabolism→ ↑levels in circulation and ↑deposition of LDL in endothelial lesions.
·↑Levels of small, dense LDL (more atherogenic than large, buoyant LDL)
·↑Oxidised LDL
·↑Lp(a) in type II (acute phase reactant)

Hypothyroidism

↑LDL, ±↑TG, ±↑ HDL
·↓Rate of catabolism of LDL
·↓Function of hepatic LDL receptors
·↑Homocysteine (→ oxidation of LDL and insulin resistance)

Cushings Syndrome

Cortisol → hyperglycaemia, by stimulating gluconeogenesis → chronic stimulation of islets of Langerhans. Eventually, the production of insulin falls → diabetic state with ↑VLDL levels.
Anti-insulin effect of cortisol on adipose tissue → breakdown of TG and release of FFA into circulation
Cortisol → truncal obesity which predisposes to development of Type II diabetes.

Lifestyle

Habitual excessive alcohol ingestion, obesity and lack of exercise are lifestyle risk factors for hyperlipidaemia

Appropriate investigations to exclude secondary hyperlipidaemia

Fasting blood glucose	**Diabetes, Cushings syndrome**
U&E	**Chronic renal failure**
PCR	**Nephrotic syndrome**
LFT	**Obstructive jaundice**
	Hepatitis
	Alcoholism
TSH	**Hypothyroidism**

Obesity and Type II Diabetes

The expanded adipose tissue mass acts as an endocrine organ, secreting into the circulation:

1. Free Fatty Acids
2. Cytokines
   - Tumour necrosis factor (TNF)
   - Interleukin-6 (IL-6)
   - Resistin - a cytokine which decreases tissue sensitivity to insulin
3. Plasminogen activator inhibitor (PAI-1)

At the same time, there is ↓secretion of two substances normally secreted by adipose tissue, both of which are insulin sensitising, namely

1. Adiponectin
   and
2. Leptin

Free Fatty Acids (FFA)
The ↑levels of FFA arriving at the liver inhibit the formation of citrate from oxaloacetate and acetyl CoA (citric acid cycle) , instead promoting conversion of oxaloacetate to phosphoenolpyruvate, a precursor of glucose in the gluconeogenesis pathway.

Glucose
Gluconeogenesis ↑
Phosphoenolpyruvate
FFA +ve→ ↑
Oxaloacetate + Acetyl CoA→ Citrate
↑
FFA −ve

This results in ↑blood glucose level which stimulates insulin release from the pancreas. Insulin however, is prevented from performing its function of promoting transport of glucose into tissue cells, due to the anti-insulin effects of FFA and cytokines (and the loss of the insulin-sensitising effect of adiponectin and leptin) Net result is ↑blood levels of glucose and insulin.

Fate of FFA arriving at the liver:
Excessive amounts of FFA arriving at the liver result in ↑ production of VLDL. These enter the circulation but due to the anti-insulin effects and loss of insulin-sensitising effects mentioned above, the VLDL are not able to offload their cargo of TG due to the ↓activity of the enzyme, lipoprotein lipase. Net result is ↑ levels of VLDL which remain in the circulation for longer.

Enhanced function of the enzyme, hormone sensitive lipase inside adipose tissue cells, results in ↑breakdown of TG inside fat cells, with pouring out of FFA into the circulation.

Increased blood glucose levels:
Blood glucose levels increase due to promotion of gluconeogenesis and to impaired insulin function. LDL become glycosylated → impairment of their metabolism, longer circulation time and ↑ deposition in areas of endothelial damage.

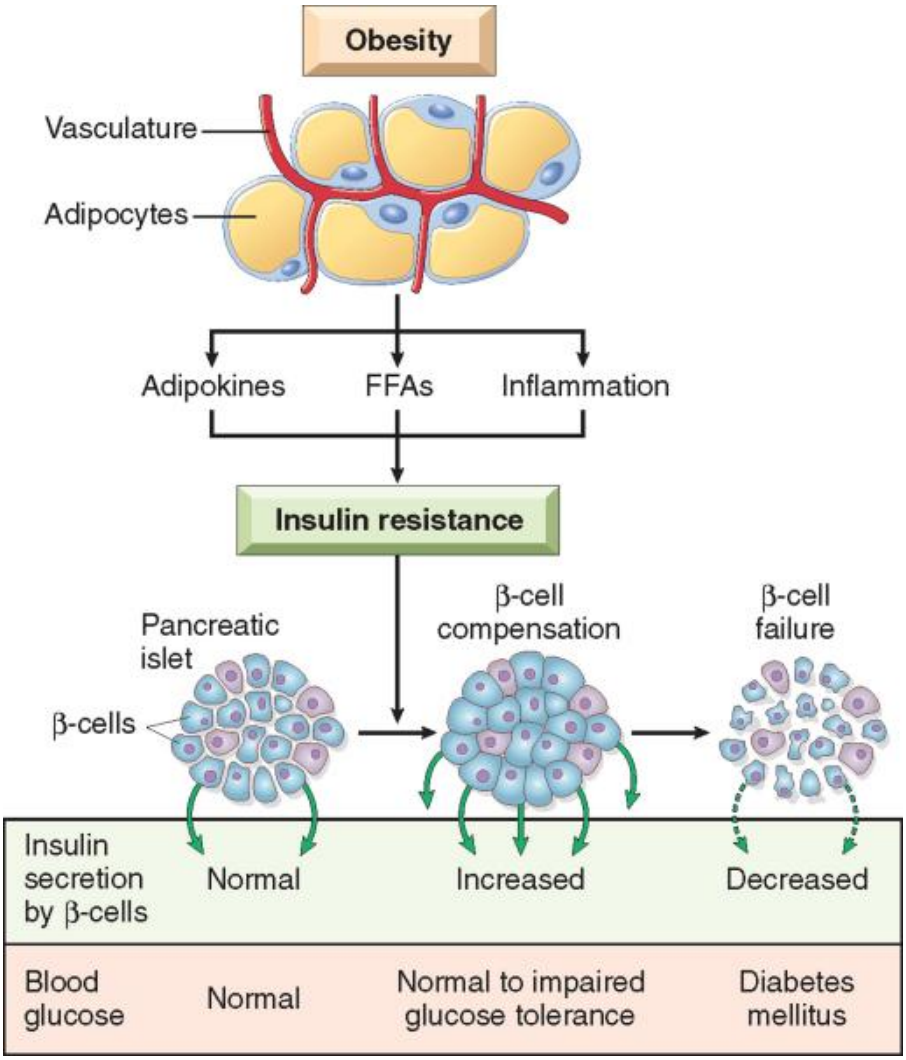
The cytokines, IL-6 and TNF stimulate production of acute phase proteins in the liver, including CRP, fibrinogen, prothrombin and Lp(a). They also stimulate release of plasminogen activator inhibitor (PAI) from adipose tissue.

A prothrombotic and proinflammatory state is created which in the milieu of the lipid abnormalities (↑VLDL, ↑glycosylated LDL, ↑small dense LDL, ↑ oxidised LDL, ↑Lp(a), ↓HDL) predisposes to intimal damage and plaque formation.

Hypertension in Type II Diabetes

Insulin promotes development of hypertension by:
◦Enhancing sodium reabsorption in the kidneys
◦Stimulating the sympathetic nervous system

Cytokines and FFA may also contribute to production of hypertension.



Development of type 2 diabetes. Insulin resistance associated with obesity is induced by adipokines, (cytokines released from adipose tissue) free fatty acids, and chronic inflammation in adipose tissue. Pancreatic β cells compensate for insulin resistance by hypersecretion of insulin. However, at some point, β-cell compensation is followed by β-cell failure, and diabetes ensues.

Glucose Metabolism

The liver has the important role of maintaining a steady blood glucose level, so that tissues which are dependent on glucose as an energy source, such as the *brain* and *red blood cells*, have a constant supply.

When glucose is plentiful, it is converted to glycogen and stored in the hepatocytes. When the capacity is reached for storing glycogen, any surplus glucose is converted to triglyceride (TG) (aka triacylglycerol)

Triglyceride consists of: **1 x Glycerol**
3 x Fatty acids (FA)

Glycerol is derived from **Glyceraldehyde -3- P** (from the glycolytic pathway)

FA are derived from Acetyl-CoA, which in turn is derived from pyruvate, one of the end-products of the glycolytic pathway. CoA is supplied by the vitamin, Pantothenic Acid.

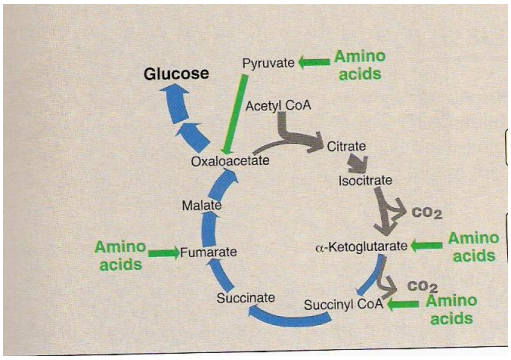
Pyruvate
↓ ← CoA -Pantothenic Acid
Acetyl CoA

Acetyl CoA is the first step along the path towards fatty acid synthesis. (Acetyl CoA combines with Malonyl CoA and then variable lengths of Acetyl CoA chains are added to this to form the various fatty acids.
Thus, all components of triglycerides can be derived from products of glycolysis.

When the glucose level in the blood is too low, glycogenolysis takes place and then, if required, gluconeogenesis, that is, the formation of glucose from amino acids and TG.

Glucose from fats: TG are broken down to FA + Glycerol; the Glycerol is converted to Glyceraldehyde -3-P, which can then, in the reverse direction of the glycolytic pathway, be converted to glucose.

Glucose from amino acids: Amino acids are converted back to their α-keto acid equivalents and then directly or via the citric acid cycle, are metabolised to oxaloacetate, thence to phospho-enol-pyruvate and then upwards (reverse glycolysis) to form glucose. All the amino acids except leucine and lysine are capable of forming glucose in this way.



Investigations in Diabetes Mellitus (DM)

Investigations which aid in diagnosis of suspected DM

1. Urine dipstix for glucose and ketones, and protein

2. Fasting blood glucose ≥ 7 mmol/L

3. Random blood glucose > 11 mmol/L

If results equivocal, oral Glucose Tolerance Test may be required.

Investigations which aid in classification of the type of DM

◦ **Serum insulin** or **C-peptide** levels

C-peptide (connecting peptide) forms part of the pro-insulin molecule, and can thus be used as a direct measure of the patient's insulin level in a 1:1 ratio. (It is technically easier to measure than insulin is) Measurements do not always distinguish type 1 from type 2 DM, but a low C-peptide level characteristically occurs in Type I diabetes, while in Type II there may be a normal or ↑level.

◦ **Islet cell antibodies** measured at the time of diabetes onset may be useful if the type of DM is not clear.

Investigations to assess possible complications of DM

◦ ***Urea, creatinine, electrolytes*** to assess renal function and electrolyte status -hyponatraemia and hyperkalaemia characteristic of DKA
◦ ***Fasting lipid screen*** - ↑triglycerides characteristic in poorly controlled type II diabetes
◦ ***Baseline and Stress ECG*** - ↑risk IHD
◦ ***Arterial Blood Gas Analysis*** – high anion gap acidosis in DKA

In suspected Hyperglycaemia, Hyperosmolar Syndrome - HHS aka HONK:

· ***p-Osmolality*** – markedly ↑due to profound dehydration, ↑urea and ↑↑glucose

(Very mild / no acidosis; ketones usually negative in urine)

The Metabolic Syndrome

The NCEP (National Cholesterol Education Program) Adult Treatment Panel III defined metabolic syndrome as the occurrence of ≥ three of the following criteria:

- **Hypertriglyceridaemia** (fasting triglyceride level ≥1.7mmol/L)
- **Low HDL levels**
- **Insulin resistance** (fasting glucose ≥6.1mmol/L)
- **Truncal obesity** (waist circumference:>102cm in men, >88cm in women)
- **Hypertension** (BP ≥130/85mmHg or documented use of antihypertensive therapy)

Patients often have ↑ levels of lipid-depleted LDL (sometimes referred to as "small, dense LDL")

and substantially increased CHD risk.

The metabolic syndrome affects ~25% of adults and is common in CHD patients; hence, identification of moderate hypertriglyceridaemia in a patient, even if the total cholesterol level is normal, should trigger an evaluation to identify this disorder

Metabolic syndrome is not a disease, but a cluster of metabolic disturbances

Insulin resistance (and perhaps also hyperinsulinaemia) is considered to be a key pathogenetic factor in the development of other features of metabolic syndrome, such as abnormal glucose tolerance, hyperlipidaemia and hypertension. Central obesity promotes insulin resistance, although *insulin resistance has a strong genetic component* and not all insulin-resistant individuals are overweight

Disturbances of blood glucose levels

Hyperglycaemia

Hyperglycaemia occurs in two main settings:

1. Patients without previously documented Diabetes Mellitus (DM)

◦ New onset DM (Type I or type II)

◦ Gestational diabetes

◦ Acute stress

Trauma, surgery
Acute MI, CVA
Severe illness, including infection

◦ Endocrine disorders

Steroid administration
Cushings disease
Acromegaly

◦ Drugs

Thiazides
Beta blockers
Phenytoin
Opiates

◦ Pancreatic injury

Pancreatitis (acute or chronic)
Haemochromatosis ("Bronze diabetes")

◦ Factitious

Taking blood from a vein into which is being infused a dextrose containing solution

2. Patients with documented Diabetes Mellitus (DM)

The underlying precipitants of elevated blood glucose in these patients include:

◦ Acute stress

Intercurrent illness
Surgery, trauma

◦ Drugs

e.g.Thiazides

◦ Non-compliance with diet or hypoglycaemic medication

Hypoglycaemia

- Drugs
  - Insulin
  - Sulphonylureas
  - Alcohol
- Critical illness
  - Hepatic failure
  - Renal failure
  - Overwhelming sepsis with organ failure
  - Starvation
- Hormonal deficiencies
  - Cortisol
  - Growth hormone
  - Epinephrine
- Insulinoma
- Other
  - Post-prandial hypoglycaemia

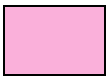
Location of the site of a myocardial infarct

Std I	aVR	V1	V4
Std II	aVL	V2	V5
Std III	aVF	V3	V6

	Arterial supply of these anatomical areas
Lateral LV (upper part)	Left circumflex artery (LCX)
Inferior LV	Posterior descending artery (usually from RCA)
Endocardium LV	Left coronary artery (LAD ±LCX)
Septum	Left anterior descending artery (LAD)
Lateral LV (lower part)	Diagonal branch of LAD

Std I	aVR	V1	V4
Std II	aVL	V2	V5
Std III	aVF	V3	V6

Arterial supply



Posterior LV

Posterior descending artery (usually from RCA)

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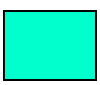
Std I	aVR	V1	V4R
Std II	aVL	V2	V5
Std III	aVF	V3R	V6

Arterial supply



Right ventricle

Right coronary artery

Pulmonary Function Tests – Learning Objectives

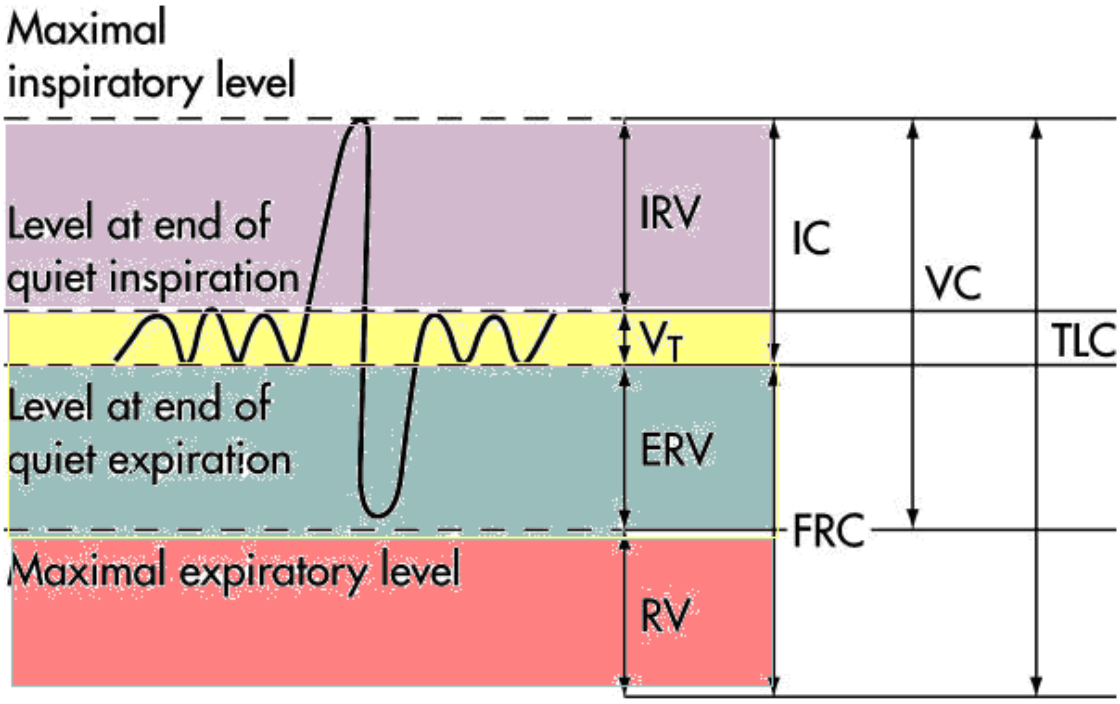
Essential

- ✓ Understand what a PFT measures: static lung volumes, spirometry, Flow Volume Loop, DLCO.
- ✓ Accurately recognise an obstructive pattern using asthma and COPD as clinical examples
- ✓ Accurately recognise a restrictive pattern using asbestosis as a clinical example
- ✓ Be able to perform spirometry on a patient (Pulmonary lab at Mater; opportunities on rural term)
- ✓ Accurately identify the major structures visible on a PA and lateral CXR (Diagnostic Imaging Pathways website)

Static Lung Volumes

Static lung volumes are determined using methods in which *airflow velocity* does not play a role. They reflect the elastic properties of the lungs and chest wall.
The sum of two or more lung volumes constitutes a lung capacity.
The subdivisions and capacities are expressed in liters.
Four *volumes* are measured (tidal volume, inspiratory reserve volume, expiratory reserve volume, and residual volume). Using these four measurements of volume, four *capacities* are calculated

Subdivisions of Lung Volume



Inspired and expired volumes during normal quiet breathing.
Most lung volumes and capacities can be measured by spirometry.
(TLC, FRC, and RV are not determined by spirometry.)
ERV, expiratory reserve volume
FRC, functional residual capacity
IC, inspiratory capacity
IRV, inspiratory reserve volume
RV, residual volume
TLC, total lung capacity
VC, vital capacity
V_T, tidal volume

1 Tidal volume (TV) is the volume of air that is inhaled or exhaled with each normal respiratory cycle.

2 Inspiratory reserve volume (IRV) is the maximal volume of air that can be inhaled after a normal tidal inhalation.

3 Expiratory reserve volume (ERV) is the maximal volume of air that can be exhaled after a normal tidal exhalation

4 Residual volume (RV) is the volume of air remaining in the lung at the end of a maximal expiration.
The RV normally accounts for 25% of total lung capacity (TLC).
In restrictive lung disorders, RV decreases less than the other volumes.
In COPD and asthma, the increase in TLC is due largely to an increase in residual volume.

5 Functional residual capacity (FRC) is the volume of air in the lungs after a normal tidal exhalation. It is the sum of the ERV and RV.
FRC = 40% of TLC.

6. Inspiratory capacity (IC) is the maximal volume of air that can be inhaled after a normal tidal exhalation.
IC = sum of TV and IRV.

7. Vital capacity (VC) is the maximum volume of air that can be expired slowly after a full inspiratory effort.
The subdivisions of the VC include TV, inspiratory reserve volume (IRV), and expiratory reserve volume (ERV).
VC = IRV+TV+ERV
Also, VC = TLC - RV

8. Total lung capacity (TLC) is the volume of air in the lung at the end of a maximal inspiration.
TLC may be calculated in one of two ways:
(1) TLC = RV + VC
(2) TLC = FRC + IC.

Forced Vital Capacity, FEV1 and FEF 25% – 75%

Forced vital capacity (FVC)
The FVC is the volume of air expired *with maximal force* following maximal inspiration. The VC can be much greater than the FVC in patients with airways obstruction. The FVC manoeuvre can result in premature closure of terminal airways with resultant air trapping, so the true RV is not reached.

Forced Expiratory Volume in the first second (FEV1)
The FEV1 is the volume of air expired in the first second of the FVC manoeuvre.
FEV1 = 75-80% of FVC

Forced expiratory flow during the middle half of the FVC (FEF 25% – 75%)
The mean forced expiratory flow during the middle half of the FVC (FEF 25% – 75%) is the slope of the line that intersects the spirographic tracing at 25% and 75% of the FVC. The FEF 25% - 75% is less effort dependent than the FEV1 and is a more sensitive indicator of small airways obstruction (airways <2mm in diameter). The line approaches the horizontal due to prolongation of the expiratory phase in airways obstruction.

Flow Volume Loops

The flow-volume loop is recorded by a spirometer during a forced inspiratory and expiratory VC manoeuvre. The shape reflects the status of the lung volumes and airways throughout the respiratory cycle.

Peak expiratory flow rate is sometimes used to estimate degree of airways obstruction, but *is very dependent on patient effort*.

The small airways (diameter < 2mm), constitute < 10% of the total airway resistance, but their surface area is large. Disease affecting primarily the small airways can be extensive, yet not affect tests such as FEV1.

Expiratory flow rates over the lower 50% of the FVC (i.e. approaching residual volume) are sensitive indicators of small airways disease, such as early obstructive and interstitial lung disease.

A: Normal

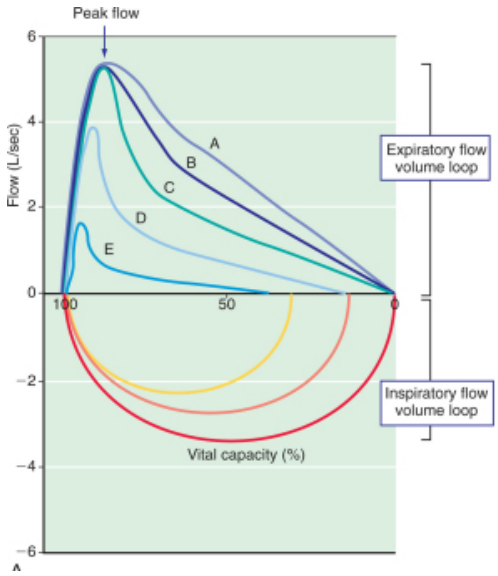
Inspiratory limb of loop is symmetric and convex. Expiratory limb is linear.

B. Restrictive disease (e.g. sarcoidosis, kyphoscoliosis)

Configuration of loop is narrowed because of ↓lung volumes but shape is basically normal. At comparable lung volumes, flow rates are normal. (Actually ↑ because airways held open by ↑elastic recoil)

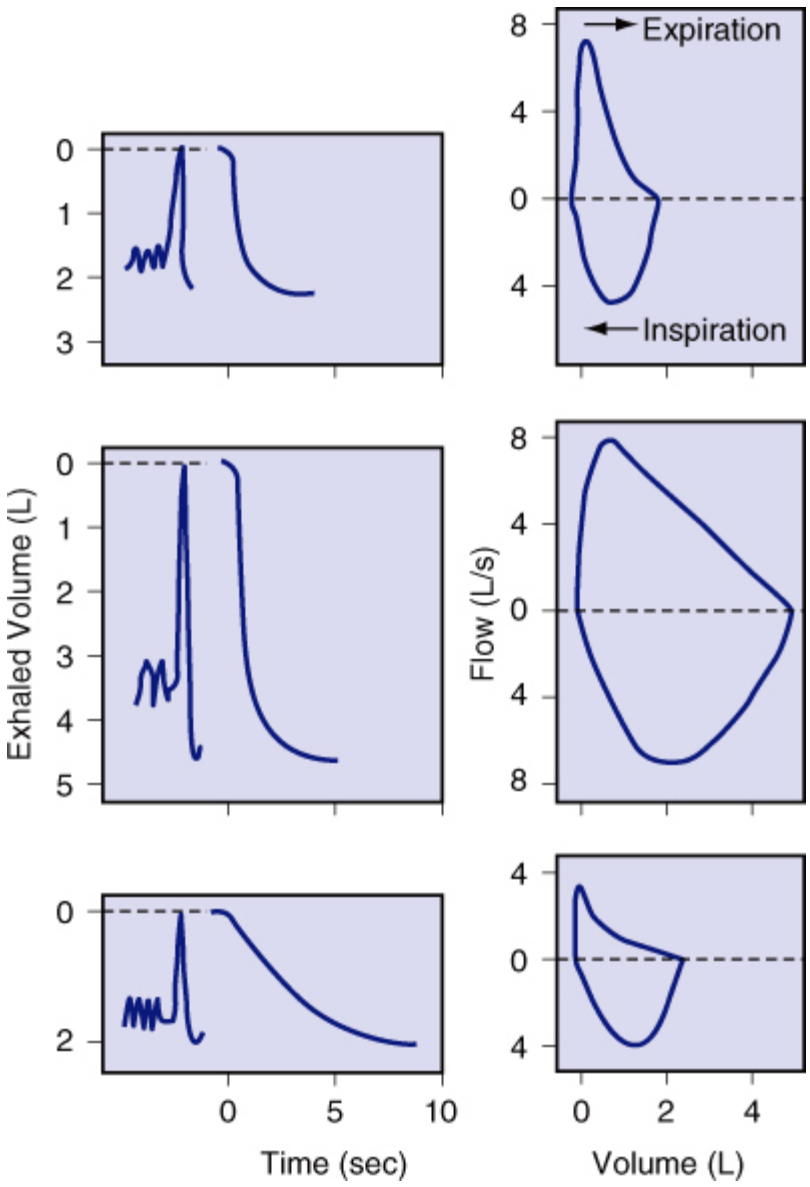
C. COPD, asthma

All flow rates ↓, but particularly expiratory flow rate is ↓↓.



Spirometric flow-volume loops.
A is an expiratory flow-volume loop of a nonasthmatic, without airflow limitation.
B to E are expiratory flow-volume loops in asthmatic patients with increasing degrees of airflow limitation (B is mild; E is severe). Note the "scooped" or concave appearance of the asthmatic expiratory flow-volume loops; with increasing obstruction, there is greater "scooping."

Spirograms and flow-volume loops



Top	Restrictive ventilatory defect
Middle	Normal subject
Bottom	Obstructive ventilatory defect

Causes of Restrictive Ventilatory Defects

Interstitial Lung Disease
Interstitial pneumonitis
Fibrosis
Pneumoconiosis
Granulomatosis e.g. sarcoidosis
Pulmonary oedema

Space-Occupying Lesions
Tumour
Cysts

Pleural Diseases
Pneumothorax
Hemothorax
Pleural effusion, empyema

Chest-wall Diseases
Injury
Kyphoscoliosis
Spondylitis

Extrathoracic Conditions
Obesity
Peritonitis
Ascites
Pregnancy

Carbon Monoxide Diffusion Test (DLco)

Whereas spirometry measures the mechanical properties of the lungs, the lung diffusing capacity test (DLco) measures the ability of the lungs to perform gaseous exchange.
The single breath DLco test requires the patient to inhale a gas consisting of:

Helium	10%
Carbon Monoxide	1000 ppm
Air	balance

The inhaled gas is held in the lungs for 10 seconds, during which time the carbon monoxide diffuses across the respiratory membrane into the pulmonary capillary blood. The helium does not diffuse.
During exhalation, a portion of the breath representative of alveolar air is collected in a sample collection system, and the carbon monoxide concentration in this sample is determined.
The difference between the inspired and expired carbon monoxide concentrations is calculated, and the diffusing capacity of the lungs determined.
(The difference between the two values = the amount of carbon monoxide which has crossed from alveolus → pulmonary capillary blood)

Average result for a young healthy male = 17 ml/minute

This test can be of great diagnostic benefit in lung disorders not detectable by spirometry or chest Xray. The ability of the lungs to pass oxygen from alveoli → pulmonary capillary blood can be affected by damage to or loss of respiratory membrane as in emphysema, and by thickening of the membrane by fibrosis or inflammation (interstitial lung disease e.g. asbestosis)
The DLco test is more sensitive than spirometric measurements and chest Xray for the detection of interstitial lung disorders.

Causes of ↓ DLco

Interstitial lung disease
Emphysema
Severe anaemia
Smoking

Causes of ↑ DLco

Polycythaemia
Early left ventricular failure

NORMAL VALUES

Full Blood Count (FBC)	UNITS	REFERENCE RANGE
Haemoglobin	g/L	115 – 160 F 135 – 180 M
White Cell Count	x 10^9 /L	4.0 – 11.0
Platelets	x 10^9 /L	140 - 400
Haematocrit		0.33 – 0.47 F 0.35 – 0.51 M
Red cell Count	x 10^{12} /L	3.8 - 5.2 F 4.5 - 6.0 M
MCV	fL	80 - 100
MCH	pg/cell	27 – 33
Reticulocyte Count	%	0.5 – 2.0

Differential count		
Neutrophils	x 10^9 /L	2.0 – 8.0
Lymphocytes	x 10^9 /L	1.0 – 4.0
Monocytes	x 10^9 /L	0.1 – 1.0
Eosinophils	x 10^9 /L	< 0.60
Basophils	x 10^9 /L	< 0.20
Bands	x 10^9 /L	< 0.90
Metamyelocytes	x 10^9 /L	< 0.01

Urea & Electrolytes (U&E)		
Sodium	mmol/L	135 - 145
Potassium	mmol/L	3.2 – 4.5
Chloride	mmol/L	100 - 110
Bicarbonate	mmol/L	22 – 33
Calcium	mmol/L	2.15 - 2.60
Phosphate	mmol/L	0.7 – 1.4
Magnesium	mmol/L	0.7 – 1.0
Uric Acid	mmol/L	0.12 – 0.45
Urea	mmol/L	3.0 – 8.0
Creatinine	µmol/L	70 – 120
eGFR	ml/min	>90
Urea:Creatinine Ratio		40 - 100
Lactate	mmol/L	0.7 - 2.5
Anion Gap	mmol/L	4 - 13

Liver Function Tests (LFT)		
Protein (Total)	g/L	62 - 83
Albumin	g/L	33 - 47
Globulin	g/L	25 - 45
Bilirubin (Total)	µmol/L	< 20
Bilirubin (Conjugated)	µmol/L	< 4.0
Alkaline Phosphatase	U/L	40 - 110
Gamma-GT	U/L	<50
Alanine Transaminase	U/L	<45
Aspartate Transaminase	U/L	<40
Lactate Dehydrogenase	U/L	110 -250
Amylase	U/L	25 -130
Creatine Kinase	U/L	< 200

Haptoglobin	**g/L**	**0.36 – 1.95**
Caeruloplasmin	**mg/dL**	**23 - 43**
C-Reactive Protein	**mg/100ml**	**≤ 0.8**
Erythrocyte Sedimentation Rate (ESR)	**mm/hr**	**<14 M**
		<12 F

Fasting Lipids

Cholesterol	**mmol/L**	**< 5.5**
Triglyceride	**mmol/L**	**< 2.0**
HDL Cholesterol	**mmol/L**	**0.9 – 1.6**
LDL Cholesterol	**mmol/L**	**2.0 – 4.2**
VLDL Cholesterol	**mmol/L**	**calculated**
Homocysteine	**µmol/L**	**≤ 13**
Osmolality (plasma)	**mmol/kg**	**275 – 295**
Osmolality (urine)	**mmol/kg**	**100 - 1000**

Arterial Gas Parameters

PH		**7.35 -7.45**
pCO_2	**mmHg**	**35 - 45**
pO_2	**mmHg**	**75 - 100**
Oxygen saturation	**%**	**94 – 98**
Bicarbonate	**mmol/L**	**22 – 33**
p50	**mmHg**	**24 – 28**
Base Excess	**mmol/L**	**-3.0 to +3.0**

Blood Glucose

Fasting	**mmol/L**	**3.0 – 7.8**
Random	**mmol/L**	**≥ 11.1**

Coagulation Screen

Prothrombin Time	**sec**	**9 - 14**
APTT	**sec**	**25 - 38**
INR		**0.9 – 1.3**
Fibrinogen	**g/L**	**1.5 – 4.0**
D-dimer	**mg/L**	**< 0.50**
Fibrin Degradation Products (FDP)	**not done at TTH pathology lab**	

Iron Studies

Serum Iron	**µmol/L**	**10 - 30**
Transferrin	**g/L**	**1.6 – 3.0**
Transferrin IBC	**µmol/L**	**40 - 75**
Transferrin Saturation	**%**	**15 - 45**
Serum Ferritin Assay	**µg/L**	**10 - 200**
Vitamin B12	**pmol/L**	**> 210**
Red Cell Folate	**nmol/L**	**> 630**

Thyroid Function Tests

Thyroid stimulating hormone (TSH)	**mU/L**	**0.15 – 3.5**
Thyroxine (T4)	**pmol/L**	**10 - 27**
Triiodothyronine (T3)	**nmol/L**	**1.0 – 2.6**

Urine Tests

Albumin:Creatinine Ratio	**g/mol**	**< 2.6 M** **< 3.6 F**
Protein:Creatinine Ratio	**g/mol**	**< 15**

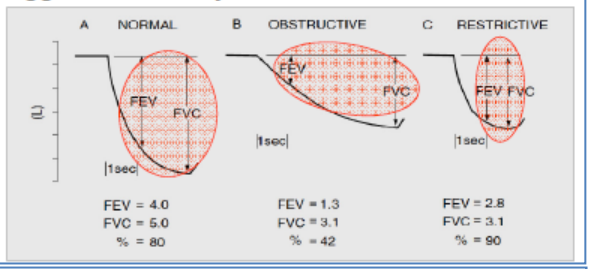
PFT Interpretations

PFTs – Pulmonary Function Tests:

- **FVC** - Forced Vital Capacity – Liters - diagnosis of obstructive and restrictive diseases.
- **FEV1** - Forced Expiratory Volume in One Second – obstructive/restrictive diseases.
- **FEV1/FVC** - FEV1 Percent (FEV1%) - it indicates what percentage of the total FVC was expelled from the lungs during the first second of forced exhalation. critically important in differentiating obstructive from restrictive diseases.
- **FEV3** - Forced Expiratory Volume in Three Seconds – equal to FVC in normal.
- **FEV3/FVC** - FEV3% - normal is 1 or 100%
- **PEFR** - Peak Expiratory Flow Rate - this is maximum flow rate achieved by the patient. For monitoring response to treatment.
- **FEF** - Forced Expiratory Flow - is a measure of how much air can be expired from the lungs (liters/second or liters/minute). The FVC expiratory curve is divided into quartiles and therefore there is a FEF that exists for each quartile. The quartiles are expressed as FEF25%, FEF50%, and FEF75% of FVC.

PFT: interpretation:

- Check FVC & FEV1 – normal → normal PFT
- If FVC and/or FEV1 are low - Pathology.
- Check FEV1/FVC ratio:
- FEV1/FVC% (<70%) - Obstructive.
- FEV1 /FEVC% (>80%)- Restrictive.
- An improvement in FEV1 of 200ml or more after bronchodilator suggests versibility → Asthma.



Restrictive vs Obstructive

Restrictive	Obstructive
• Interstitial - (stiff lung)	• Obstructive (soft lung)
• Increased tissue	• Destruction of tissue.
• Relatively normal FEV1:FVC ratio	• Low FEV1:VC ratio
• Normal PEFR.	• Low PEFR.
• Types:	• Types:
•Acute – ARDS,Viral.	–Localised & Diffuse
•Chronic - pneumoconioses & sarcoidosis, Int. fibrosis.	–Reversible & progressive.
	–COPD
	–Asthma
	–Bronchiectasis,

6. Renal Function Tests

Essential

Pre reading

- *Normal functions of the kidney*
- *Normal anatomy of the kidney including the micro-anatomy of the nephron*
- *Function of the juxtaglomerular apparatus*
- *Normal urine: volume, pH, constituents such as: Tamm-Horsfall protein, urobilinogen*
- *Abnormal urine: proteinuria, glycosuria, ketonuria, nitrites, increased numbers of cells + casts*

In course

- Understand the clinical relevance of GFR
- Understand the staging of CKD using GFR results
- Be able to list the common causes of CKD: diabetes, glomerulonephritis, hypertension
- Understand the use of urea and creatinine levels in assessing renal function
- Understand the clinical use of the urea:creatinine ratio using clinical examples of pre renal, renal and post renal failure
- Be able to list important causes of pre renal failure: dehydration, haemorrhage
- Be able to list important causes of intrinsic renal failure: infection (glomerulo- and pyelonephritis); drugs (NSAIDs); ischaemic insult (emboli → vascular occlusion, haemorrhage → hypotension and acute tubular necrosis if prolonged)
- Be able to list important causes of post renal failure: BPH
- Understand the use of urinary PCR and ACR in assessing renal function
- Understand the physiological basis of the common electrolyte disturbances seen in renal failure: Na^+, K^+, phosphate, Ca^{++} and $HCO3^-$
- Understand 'the anaemia of renal disease'
- Understand the key clinical and biochemical features of nephrotic syndrome (proteinuria >3g/24hr; hypoalbuminaemia; hyperlipidaemia; prothrombotic state; hypogammaglubulinaemia)

Important

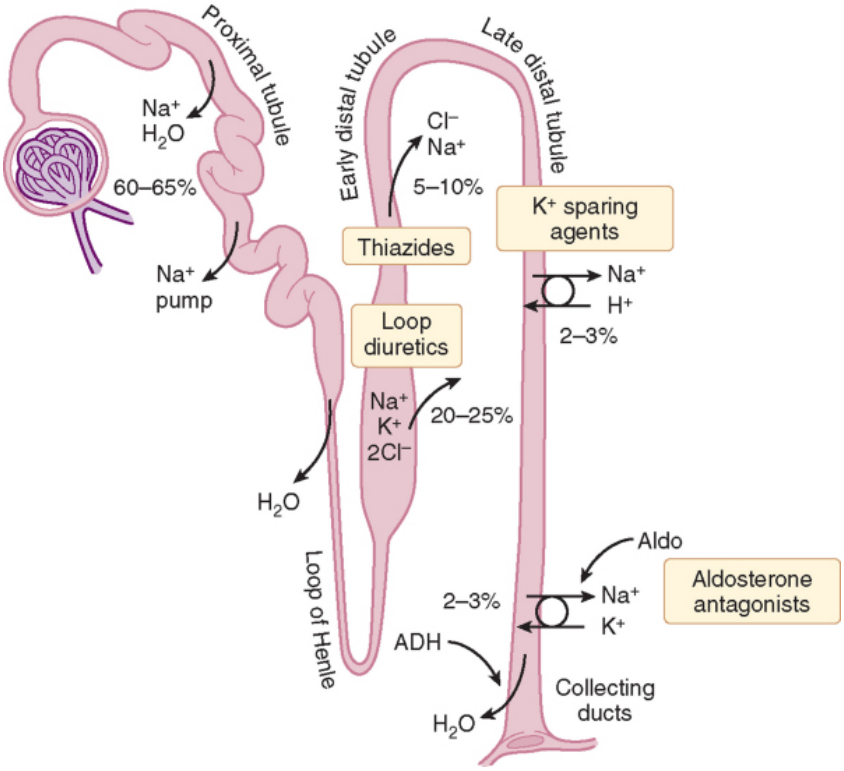
- Understand the clinical relevance of plasma hypo – and hyperosmolality using the examples of hyperosmolar non-ketotic diabetic coma, diabetes insipidus and SIADH
- Understand the clinical relevance of 24 hour urine collection (protein measurement)

Desirable

- Be able to calculate the eGFR using the Cockcroft-Gault formula

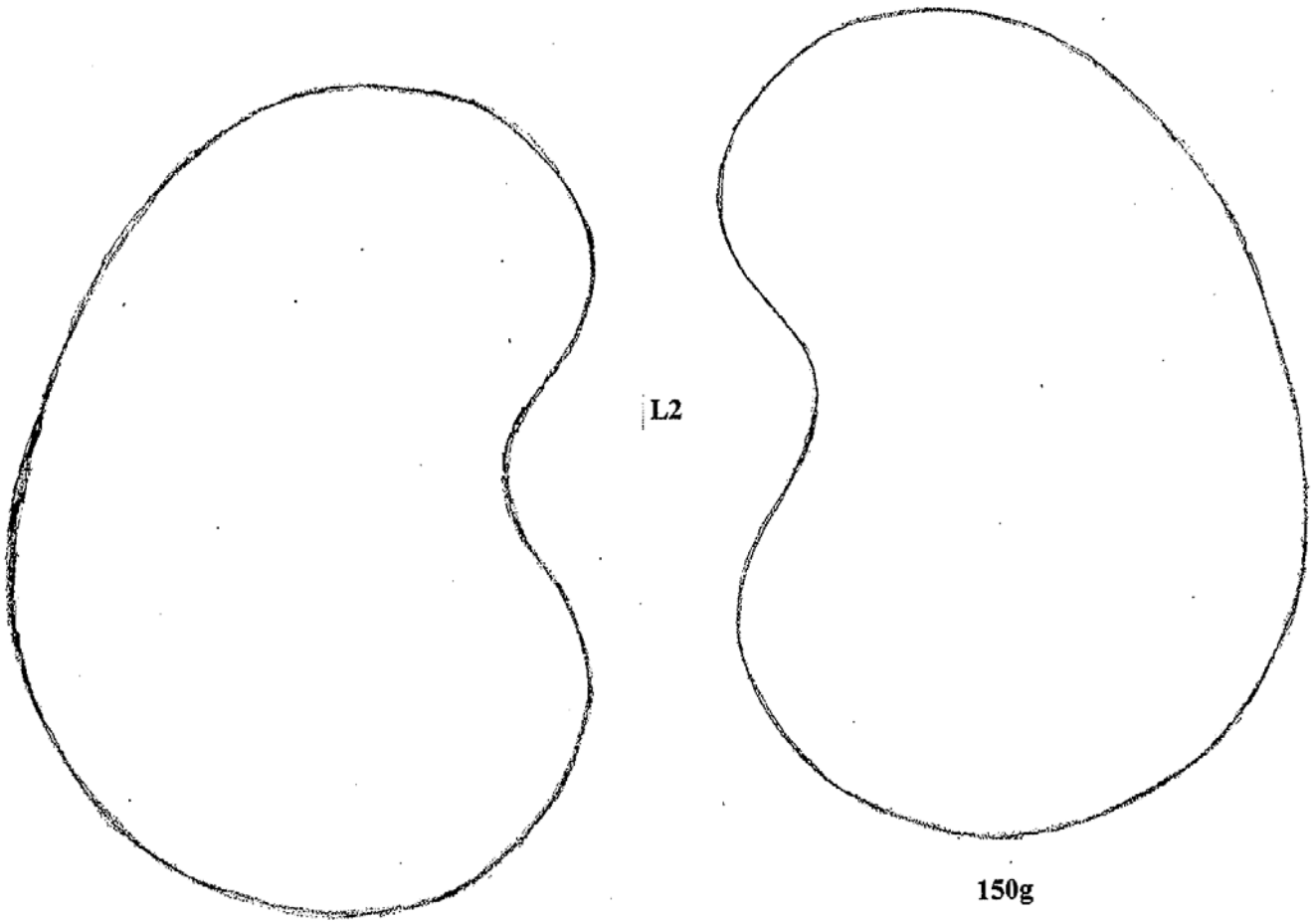
FUNCTIONS OF THE KIDNEY

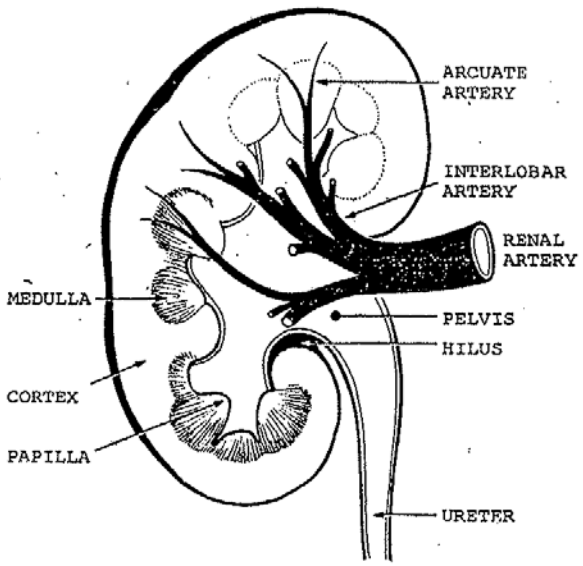
1. Excretion of metabolic waste products e.g. urea and creatinine and drugs
2. Acid:base balance
3. Maintenance of normal electrolyte levels
4. Endocrine function – erythropoietin production
5. Hydroxylation of Vitamin D to its active form
6. Maintenance of stable blood pressure
7. Maintenance of normal plasma osmolality
8. Gluconeogenesis



The Nephron

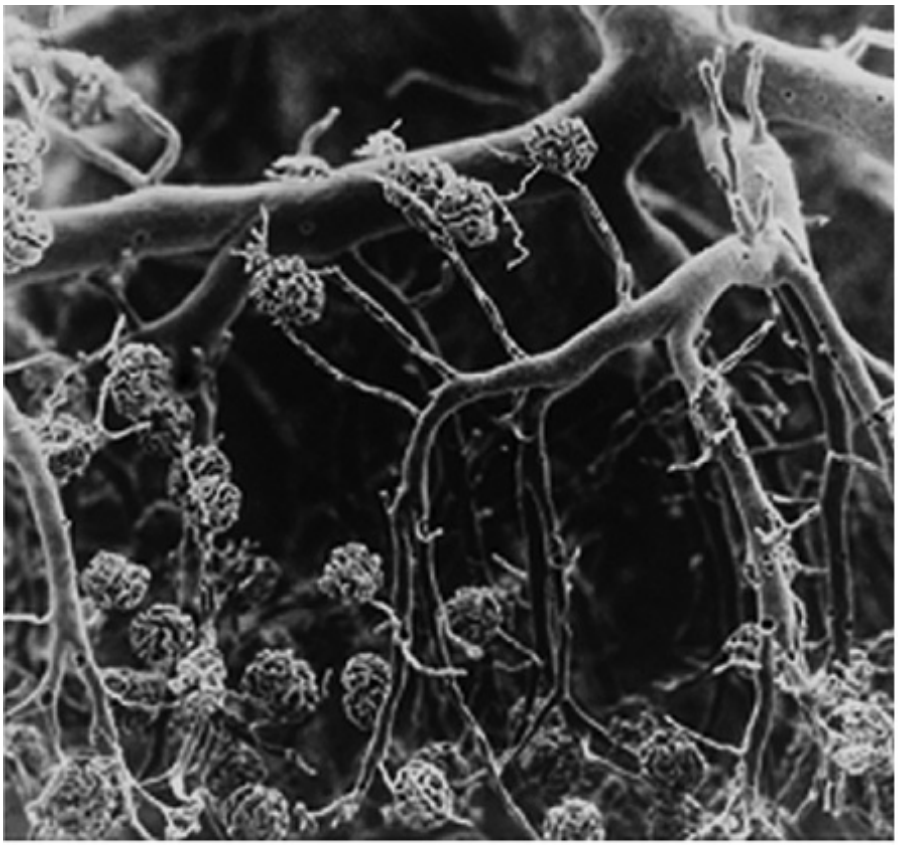
Lifesize Drawing of the Kidneys





The gross structure of the cut surface of a kidney.

Glomerular Architecture



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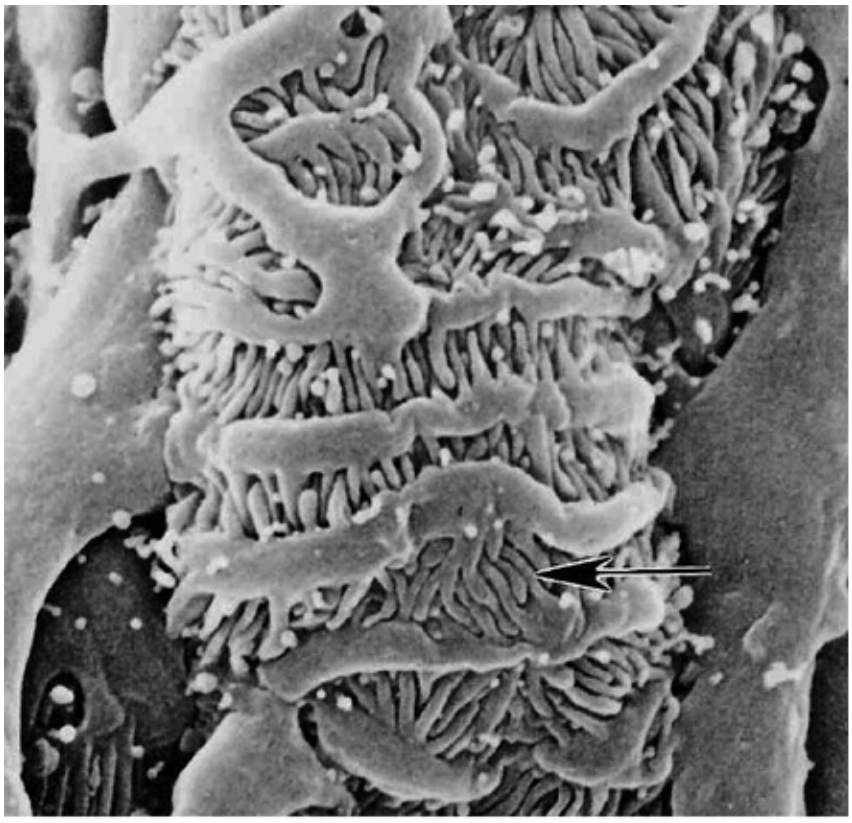

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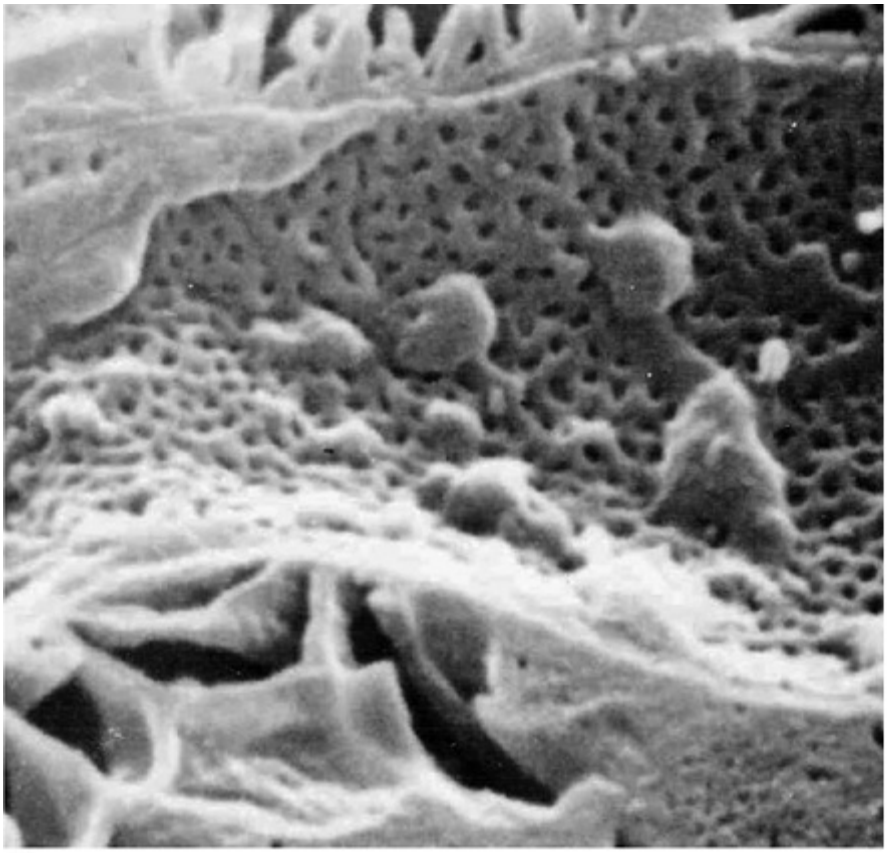

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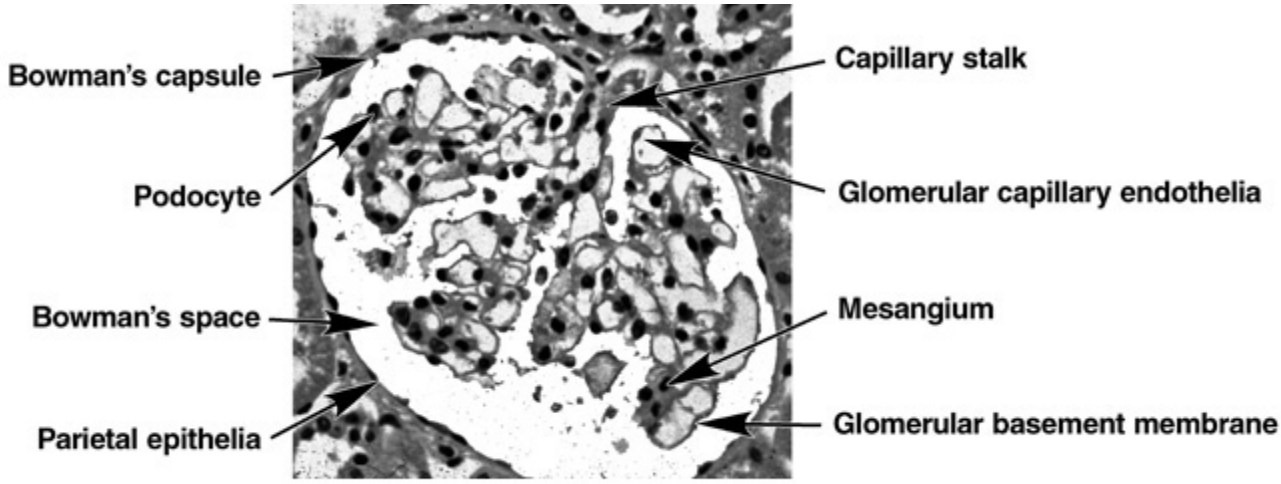


D

Glomerular architecture

A. The glomerular capillaries form from a branching network of renal arteries, arterioles, leading to an afferent arteriole, glomerular capillary bed (tuft), and a draining efferent arteriole

B. Scanning electron micrograph of podocytes that line the outer surface of the glomerular capillaries (arrow shows foot process).

C. Scanning electron micrograph of the fenestrated endothelia lining the glomerular capillary.

D. The various normal regions of the glomerulus on light microscopy

Substances exerting an important influence on the kidney

Renin

Pro-renin is formed in the juxtaglomerular cells in the afferent arterioles. When the BP falls, the slow flow of filtrate along the tubules → ↑opportunity for sodium absorption.The low sodium content in the filtrate passing along the DCT stimulates the conversion of pro-renin to renin, which enters the blood in the afferent arteriole and is then carried systemically. Renin is an enzyme which converts angiotensinogen (a plasma protein) to angiotensin I (10 amino acids); renin remains in the circulation for 30 – 60 minutes. Renin also causes vasodilatation of the afferent arteriole of the glomerulus.
As angiotensin I passes through the lungs, the angiotensin-converting-enzyme (ACE) produced there and present in the endothelial cells of the pulmonary capillaries, catalyses its conversion to angiotensin II (8 amino acids). The 2-amino acid peptide split off is known as hippuric acid.

Angiotensin II

1. Is a powerful vasoconstrictor; one of the arterioles it causes to constrict is the glomerular efferent arteriole.
2. Promotes Na^+ and H_2O retention by the kidney, acting on the PCT
3. Stimulates aldosterone release from the adrenal cortex
4. May be converted to angiotensin (1 – 7) which stimulates release of ADH by the posterior pituitary.

Aldosterone

Aldosterone is a steroid hormone produced by the adrenal cortex. Its production is stimulated by hyperkalaemia and by angiotensin II. It promotes absorption of Na^+ and H_2O by the distal nephron, and K^+ excretion. In the event of an acute shortage of aldosterone (example: haemorrhage into the adrenal), we are able to survive only a few days, becoming hypovolaemic, hypotensive and hyperkalaemic.
The more chronic manifestation of adrenal failure is known as Addison's disease, 90% of cases being autoimmune in aetiology, the other 10% caused either by infection with TB or secondary malignant deposits in the adrenal glands.

Antidiuretic Hormone (ADH/Vasopressin)

ADH is secreted by the posterior pituitary in response to ↑in plasma osmolality; the osmoreceptors in the hypothalamus shrink in response to ↑Na+ levels in the blood, causing a message to be sent to the posterior pituitary resulting in the release of ADH. ADH promotes water reabsorption in the collecting ducts. In the absence of ADH, this part of the nephron is impermeable to water, as occurs in Diabetes Insipidus. ADH (aka Vasopressin) also has a vasoconstrictor action.

The Juxtaglomerular Apparatus

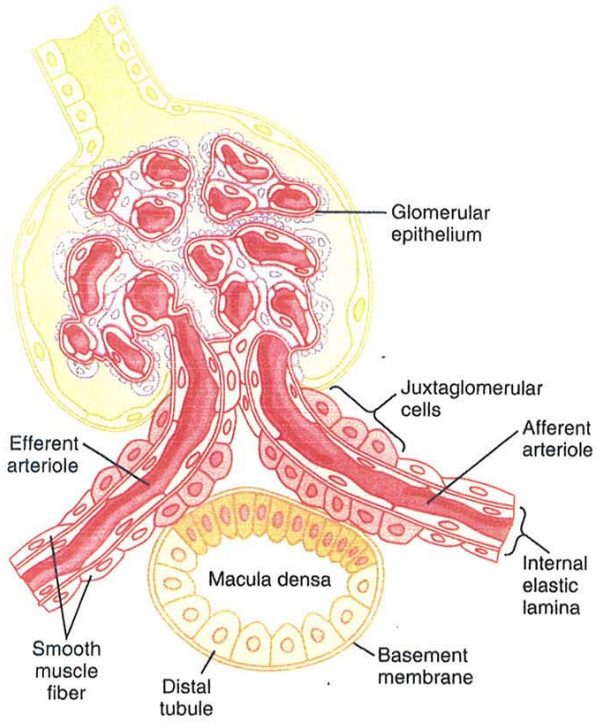
The juxtaglomerular apparatus provides a remarkable integration of tubular and glomerular structure and function.

- A modified portion of the distal convoluted tubule, the macula densa, is applied to the glomerulus at the vascular pole between the afferent and efferent arterioles.

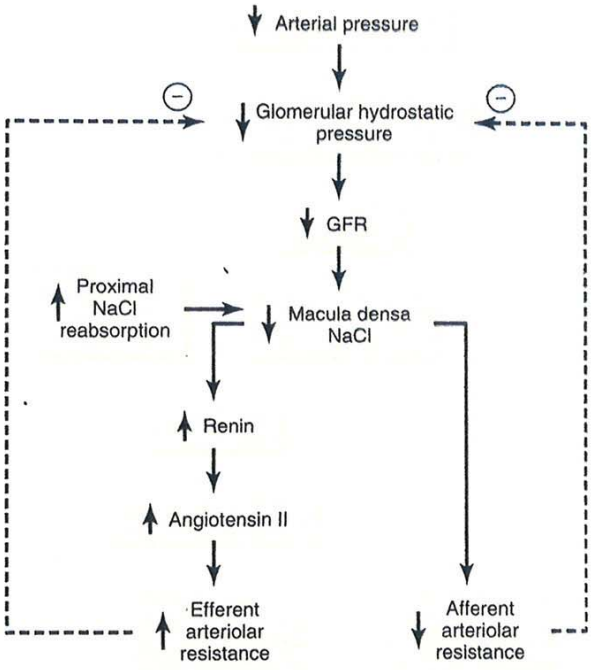
- The juxtaposed segments of the afferent and efferent arterioles contain modified smooth muscle cells (granular cells) that produce renin.

The cells of the macula densa are chemoreceptors that sense the tubular concentration of sodium chloride (NaCl). When the concentration of NaCl falls as occurs when the GFR falls (slow flow→↑ NaCl absorption by tubular cells), the cells of the macula densa sense this and send a signal to the renin producing cells of the afferent arteriole. Renin is secreted into the afferent arteriolar lumen; another consequence of this signal is dilatation of the afferent arteriole. It is not known how exactly this signal is sent.

Renin catalyses the formation of angiotensin I which is converted to angiotensin II, which in turn increases efferent arteriolar tone; this, together with the vasodilatation of the afferent arteriole, increases the GFR. Aldosterone promotes Na^+ and H_2O reabsorption by the distal nephron, thus increasing ECF volume.



Structure of the juxtaglomerular apparatus, demonstrating its possible feedback role in the control of nephron function.



Macula densa feedback mechanism for autoregulation of glomerular hydrostatic pressure and glomerular filtration rate (GFR) during decreased renal arterial pressure.

ASSESSMENT OF RENAL FUNCTION

BLOOD TESTS

▫ *Urea*

The urea level, on its own, is not a good marker for renal function
• The level only starts rising after ≥ 60% of renal function has been lost
• It is affected by several factors:

1. State of hydration
2. Amount of protein in the GIT
   - •amount of protein in the diet
   - •GIT bleeding is in effect, a high protein meal
3. Liver function (↓urea production in liver disease)

▫ *Creatinine*

The creatinine level is better as an indicator of renal function, as its level is affected (mainly) only by the muscle mass of the patient. It is produced at a rate of ~ 10 mmol/day, from the breakdown of creatine & phosphocreatine in muscle.
However, when the GFR is low, the proximal convoluted tubule secretes creatinine → ↓ plasma level which does not reflect the ↓ GFR.
Certain drugs (cimetidine, trimethoprim) can block tubular secretion of creatinine → ↑ blood levels.

▫ *Glomerular Filtration Rate (GFR)*

The GFR is a good indicator of renal function
The Cockroft-Gault formula for Creatinine Clearance is reasonably accurate & can be estimated at the bedside. (Creatinine Clearance ≡ Glomerular Filtration Rate)

$$\text{Creatinine Clearance} = \frac{\{140 - \text{age}\}\ (\text{yrs}) \times \text{weight (kg)}^*}{\text{S-creatinine } (\mu\text{mol/L})} \times 1.04\ (\text{F});\ \times 1.23\ (\text{M})$$

**The ideal body weight should be used if weight ↑↑ or ↓↓*

Staging of renal disease:

	Impairment
Stage 1 GFR >90 ml/min; other evidence of renal disease	**minimal**
Stage 2 GFR 60 – 89 ml/min	**mild**
Stage 3 GFR 30 – 59 ml/min	**moderate**
Stage 4 GFR 15 – 29 ml/min	**severe**
Stage 5 GFR <15 ml/min/dialysis	**renal failure**

▫ *Electrolytes (venous blood)*

	Units	**Reference Range**
Sodium	**mmol/L**	**135 - 145**
Potassium	**mmol/L**	**3.2 – 4.5**
Chloride	**mmol/L**	**100 - 110**
Bicarbonate	**mmol/L**	**22 – 33**
Calcium	**mmol/L**	**2.15 - 2.60**
Phosphate	**mmol/L**	**0.7 – 1.4**

▫ *Osmolality (plasma)*

mmol/L **275 – 295**

Calculated using the formula: **2 x Sodium + Urea + Glucose**

▫ *Urea:Creatinine Ratio*

This ratio is calculated using the patient's blood urea level divided by the patient's serum creatinine level

e.g. Urea 6.0 mmol/l
Creatinine 100 µmol/L
Ratio = 6/0.1
= 60
(Normal range: 40 – 100)

The urea:creatinine ratio changes depending on the type of renal failure and may therefore be helpful in diagnosis:

- Pre-renal ↑ratio*
- Intrinsic renal failure ↓ratio
- Post-renal ↑ratio

*↑Ratio especially in volume depletion (dehydration, haemorrhage), LV failure, renal artery stenosis

In pre- and post-renal failure
Urea: The passage of the filtrate through the tubules is slow, and ↑amounts of urea are reabsorbed (which will be reflected as an increase in the blood urea level). Normally, 20 – 50% of filtered urea is reabsorbed – in this situation >50 % reabsorption occurs.

Creatinine: Not only is creatinine not reabsorbed, it is actually secreted into the tubular lumen by the tubular cells when the passage of the filtrate past the tubular cells is slow. This will be reflected in the blood as a relatively low level of creatinine compared with the urea level, both of which are elevated but with an ↑ratio of urea to creatinine.

In intrinsic renal failure
Due to the intrinsic damage to the kidneys, filtration is ↓↓, so urea and creatinine accumulate rapidly in the blood, with the creatinine level tending to rise proportionately > the urea level (↓urea:creatinine ratio); this is not a reliable test in this situation, however.
A s-creatinine level > 250 µmol/L has a 90% probability for intrinsic renal failure (as distinct from pre-renal failure) and is a more reliable test here. (>2x normal creatinine level)

Other causes of change in urea:creatinine ratio
(Factors altering urea or creatinine levels per se, independently of renal failure)

↑Urea
GIT bleed (↑protein in GIT→↑urea production)
Tetracycline ↑protein catabolism
Sepsis "
Corticosteroids "

↓Urea
Impaired liver function (↓urea cycle)

Creatinine
Level depends on muscle mass. Muscle mass decreases with age, so relatively low levels of creatinine are produced daily in the elderly, along with a steady decline in renal function with age i.e. creatinine blood level will reflect a balance of ↓production and ↓renal excretion.

URINE TESTS

▫ *Urine examination*

Characteristics of normal urine

Urine Volume	1 – 1.5 L/day
GFR	100 – 120 ml/minute (↓ with age)
Protein	≤ 150 mg/day
Red Blood Cells	< 5 /low power field
White blood cells	< 10 /high power field
Urobilinogen	≤ 16 µmol/L
Osmolality	100 – 1000 mosm/kg
SG	1.002 – 1.025
pH	5 - 8
Creatinine	10 mmol/day
Urea	250 – 580 mmol/day
Sodium	0-150
Potassium	10 – 80
Calcium	2.5 – 7.5
Phosphate	15 - 50

• +ve test for blood on dipstix may = blood / haemoglobin / myoglobin
• >3 gm protein/day = nephrotic syndrome

▫ *Quantifying Proteinuria*

Measurement of albuminuria is helpful for monitoring nephron injury in many forms of CKD, especially chronic glomerular diseases, as damaged glomeruli will leak protein. While an accurate 24 hour urine collection is the gold standard for measurement of albuminuria, the measurement of albumin:creatinine ratio in a first morning urine sample is more practical to obtain and correlates well (but not perfectly) with 24 hour urine collections.

Persistence in the urine of significant amounts of albumin usually signifies chronic renal damage.
Microalbuminuria refers to the excretion of amounts of albumin too small to detect by urinary dipstick.

- ▫ It is a good screening test for early detection of renal disease in particular
  and
- ▫ may be a marker for the presence of widespread microvascular disease in general.

Just as the endothelium of the glomeruli has been so significantly damaged that it now ‘leaks’ albumin, so the endothelium of many other vascular beds may be disrupted.

If a patient has a large amount of excreted albumin, there is no reason to perform an assay for microalbuminuria, and a protein:creatinine ratio should then be performed.

Diabetic nephropathy
The onset of microalbuminuria marks a major increase in the risk of morbidity and mortality in the diabetic patient.
The onset of microalbuminuria is a signal that diabetes management needs to be revised

Measurement of albumin in the urine: the Albumin:Creatinine Ratio (ACR)

Albumin is measured as a concentration *or* as a total quantity in the specimen. It is necessary for the overall concentration of the urine or for the duration of the collection to be known. Otherwise 'normal' people could have apparently abnormal results because of very concentrated urine or a prolonged collection.

This scaling is done by:

- *creatinine*, for albumin concentration

or

- *timing* for albumin excretion rate.

The amount of creatinine we produce and excrete is determined by our muscle mass.
Creatinine is a breakdown product of creatine that acts as an energy reservoir in muscle. The more muscle we have, the more creatinine we produce.
Hence men, generally having a larger muscle mass, have higher plasma creatinine values and urine creatinine excretion than women.

The albumin creatinine ratio (ACR) scales the albumin concentration according to the creatinine concentration and allows for concentration or dilution of the urine.
Values for women are higher than men because creatinine excretion (the denominator) is lower.

In timing the urine collection scales for duration, the person voids before bed and notes the starting time of the collection. Overnight all the urine produced is collected. On rising, the person voids, collecting the urine and noting the time of completion. The laboratory calculates the duration and scales the amount of urine in the specimen by time → albumin excretion rate (AER µg/min).

Results are recorded as normo-, micro- or macro-albuminuria.

Microalbuminuria can only be detected by a laboratory or by a special urine dipstick (Micral).

Macroalbuminuria corresponds to proteinuria (≥500 mg/L of protein) and can be detected by the usual urine dipstick

Macroalbuminuria is considered more indicative of *overall kidney function* (as opposed to microalbuminuria detecting *early* damage limited to the glomerular endothelium).

Albumin:Creatinine ratio (mg/mmol) **Normal Values**
(Specimen: first voided morning urine)

	Women	Men
Normal	**0–3.5**	**0–2.5**
Microalbuminuria	**3.6–35.0**	**2.6–25.0**
Macroalbuminuria	**>35.0**	**>25.0**

Measurement of total urinary protein – the protein:creatinine ratio (PCR)

- Protein Creatinine ratio (PCR) on a spot urine specimen (preferably first voided)

The value of the PCR is determined in exactly the same way as is the ACR. In this instance, total urinary protein is assessed, not just albumin

The normal PCR is <15
The normal ACR is <3

Urine Specific Gravity

Urine specific gravity reflects the mass of 1 mL of urine compared with 1 mL of distilled water. Normal values range between 1.001 and 1.035. In settings of poor perfusion or prerenal azotaemia, urine specific gravity is high (e.g., 1.030), reflecting the kidney's ability to conserve sodium and water. With loss of concentrating ability due to acute tubular necrosis, urine specific gravity resembles plasma osmolarity (i.e., 1.010).

Urine Osmolality

Osmolality is a measure of the number of osmotically active particles in solution. It is one of the major forces that move fluid throughout the body, especially in the kidney. Theoretically, urine osmolality is physiologically superior to urine specific gravity as a test of renal function; however, the same substances and conditions that affect urine specific gravity can also affect urine osmolality

A defective urinary concentrating mechanism tends to be one of the most consistent and lasting tubular defects of ARF.

Specific gravity is a surrogate for osmolarity (normal range, 50 to 1000 mOsm/kg).

Urine osmolality as a test for distinguishing ATN from prerenal azotaemia

With urine osmolality values >500 mOsm, the positive predictive value for diagnosing prerenal azotaemia ranges from 60% to 100%.

With a value less than 350 mOsm, the positive predictive value for diagnosing acute tubular necrosis ranges from 69% to 95%.

Serum Creatinine Concentration

Creatinine, a cyclic anhydride of creatine, is a small molecule that is continuously released during skeletal muscle protein catabolism.

Serum creatinine concentration remains the most used clinical tool to assess renal function. However, serum creatinine concentration is only somewhat reliable as a sign of renal dysfunction, and GFR may be reduced by as much as 75% before elevations reach abnormal levels.

ACUTE RENAL FAILURE

AETIOLOGY - ***3 ways in which acute renal failure can be caused:***

1. Pre-Renal Causes (80% of cases)

Any cause of ineffective circulation → poor renal perfusion and ↓GFR

- •LV failure → ↓cardiac output
- •↓Circulating blood volume
  - ◦Haemorrhage
  - ◦Dehydration
- •↓Systemic vascular resistance
  - ◦Sepsis
  - ◦Liver failure
- •↑Renal vascular resistance
  - ◦Hepatorenal syndrome
  - ◦Renal artery obstruction*
  - ◦Renal vein thrombosis**

2. Intrinsic Renal Disorders (10 – 15%)

- •***Glomerular*** lesions — Acute GN
  - ◦ IgA nephropathy
  - ◦ SLE
  - ◦ Post-infectious
  - ◦ Bacterial endocarditis
- •***Tubular*** lesions
  - Ischaemia (any of pre-renal causes if inadequately treated)
  - Nephrotoxins
    - Endogenous – Myoglobin, Haemoglobin, Calcium, Uric acid, Immunoglobulin light chains
    - Exogenous - Aminoglycosides, Contrast material
- •***Interstitial*** lesions
  - ◦ Reactions to drugs – NSAIDS, antibiotics etc
  - ◦ Autoimmune diseases - SLE/MCTD
  - ◦ Pyelonephritis
  - ◦ Infiltrations - lymphoma/leukaemia
- •***Microvascular*** lesions → nephropathy
  - ◦ Vasculitis
  - ◦ Malignant hypertension
  - ◦Thrombotic microangiopathies
  - ◦Thrombo- and athero-embolism

3. Post-renal (5% – 10%)

Obstruction → anuria

e.g.
- Urethral stricture
- BPH / Ca prostate
- Ca Bladder
- Calculi
- Tumour→ compression of ureters
- Retroperitoneal fibrosis

Renal artery obstruction:

- ◦Proximal part of the renal artery in ♂>50 years (atherosclerotic basis)
- ◦Distal part of renal artery/intra-renal part in renal artery stenosis ♀20 – 50 years

These lesions cause chronic renal failure, as the obstruction impairs renal function over a period of time; acute renal failure may be precipitated if there is development of a thrombus at the site of the stenotic lesion.

****Conditions associated with renal vein thrombosis:***

Trauma
Extrinsic compression e.g. lymph nodes, tumour, AAA
Invasion of renal vein by renal cell carcinoma
Dehydration (especially in infants)
Nephrotic Syndrome
Pregnancy / oral contraception

*****Thrombo / athero-embolism*** may occur

- ◦during angiography
- ◦from intra-cardiac lesions – atrial
  - ◦thrombus secondary to AF
  - ◦atrial myxoma
- ventricular
  - ◦post MI - mural thrombus,
  - ventricular aneurysm
- ◦from atheromatous lesions of the aorta

Summary of features of acute renal failure (ARF)

History and Presentation

Pre-Renal

Variable, depending on the cause. May be preceded by a catastrophic event (e.g. post-surgical haemorrhage) → ↓BP.
Urine output ↓acutely, with a concomitant ↑in plasma urea and creatinine levels.
If the ↓renal perfusion can be rectified timeously, the renal failure may be rapidly reversed.

Intra-Renal

Many different causes affecting various parts of the nephron, so presentation depends on the cause e.g.:

- **G**lomeruli — **g**lomerulonephritis
- **T**ubules — **t**oxins, A**T**N (acute tubular necrosis)
- **I**nterstitium — **i**nfection
- **V**essels (small) — **v**asculitis, thrombo-embolism

Commonest cause is ATN following a pre-renal situation, in which blood supply to tubules is inadequate → tubular cell death.

Post-Renal

- May be a history of difficulty in passing urine.
- There may be enlarged kidneys on ultrasound if bilateral ureteral obstruction
- An enlarged bladder may be palpable if a urethral obstruction is present.

Urine Volume

Pre-Renal

Urine volume ↓ due to hypoperfusion of glomeruli. May be anuria if patient shocked ++ or bilateral vascular occlusion as in dissecting aortic aneurysm.

Intra-renal

There may be oliguria (50 – 400ml/day) or urine volume may be relatively normal (≤2.4L/day); the oliguric phase lasts on average 10 – 14 days, and may be followed by a short diuretic phase (due to persisting inability of tubules to concentrate the urine), and then a gradual return to normal urine output.

Post-renal

Anuria (<50ml/day) occurs most commonly in this situation.

Urinalysis

Pre-renal

Unremarkable – urine normal or near normal (no casts/↑cells).
↓Urinary sodium due to renin-aldosterone system activation & relatively high urinary urea (compared to intra-renal failure) because kidney function normal, just ↓perfusion pressure → ↓GFR, so urea still filtered but at ↓rate.

Intra-renal

- Haematuria and red cell casts in glomerulonephritis/vasculitis
- Epithelial casts (“muddy brown casts”) & granular casts in ATN
- Eosinophiluria in acute interstitial nephritis
- Pyuria & white cell casts in infection e.g.pyelonephritis

Post-renal

Urine normal or near normal. Possibly ↑white cells (infection) or red cells (trauma from calculi)

Blood Tests (Common to pre-, intra-, and post-renal)

Urea	Daily ↑ of 3.5 – 5.0 mmol/L/day
Creatinine	Daily ↑ of 90 - 180 µmol/L/day
Sodium	Normal /↓ if fluid overload present (as may readily occur if patient oliguric)
Potassium	↑ (↓ filtration & urinary excretion)
Calcium	↓ / Normal (↓Active Vit D, secondary hyperparathyroidism)
Phosphate	↑ (↓ filtration & urinary excretion, and secondary hyperparathyroidism)
Bicarbonate	↓ Due to metabolic acidosis (kidney unable to excrete H^+ ions) (Bicarbonate level usually in range of 15 – 20 mmol/L)
FBC	Normocytic anaemia (↓EPO, uraemic toxins)

Imaging

Renal ultrasound

To assess kidney size – if small, indicates chronic renal disease; may be ↑ in size if obstruction present

Abdominal Xray.

90% of renal calculi are visible on abdominal Xray

DIALYSIS – indications in ARF:

In ARF often used prophylactically to tide patient over till normal renal function returns.

*__Epithelial casts__ are derived from tubular lining cells that are desquamated. This occurs particularly in acute tubular necrosis → muddy, brown casts.
__Granular casts__ have a core derived from filtered plasma proteins to which cellular debris may be added, such as degenerating red cells or white cells.
__Hyaline casts__ are a normal occurrence and are derived from Tamm-Horsfall protein. They are formed mainly in the collecting ducts and there may be ↑numbers in dehydration.

Daily Urine Composition

		Normal	Acute renal failure	
			Pre-renal	Intrinsic
Volume	ml/day	1000 - 1500	<400	<400
Urea	mmol/day	350 (ave)	250	85
Creatinine	mmol/day	9 – 13	> 9	< 9
Sodium	mmol/day	100	5	25
Osmolality	mosm/L	100 - 1000	>500	<350

CHRONIC KIDNEY DISEASE (CKD)

AETIOLOGY (Commonest)

1. **Diabetes mellitus**
2. **Hypertension**
3. **Chronic Glomerulonephritis**

CKD may develop relatively rapidly over months or progress slowly over a period of years.

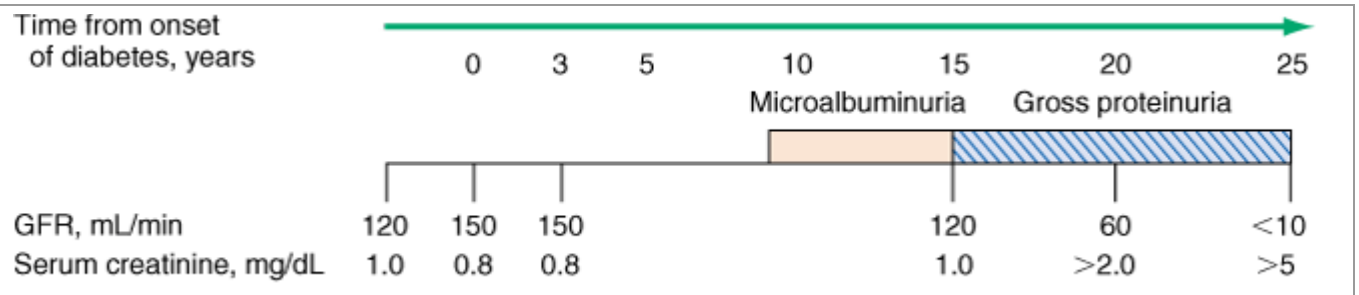
Eventually only a few nephrons remain functional, so these few have to handle all the filtered water and solutes. There is a high solute load as there is retention of waste products in the blood e.g. urea.
This high solute load causes an osmotic diuresis (similar mechanism to that which occurs in the glycosuria of diabetes mellitus). The damaged nephrons lose their concentrating ability, with the result that large volumes of urine isotonic with plasma are voided. The urine volume is usually <3L / day.

A cardinal feature of chronic renal failure is nocturia, which is a reflection of the diuresis caused by the high solute load.

1. Diabetic Nephropathy

Diabetic nephropathy is one of the commonest causes of endstage renal failure.
It is the second commonest cause of death in patients with diabetes mellitus, myocardial infarction being the commonest.

Albuminuria may already be present in type II diabetes at time of diagnosis, owing to the prolonged asymptomatic period of hyperglycaemia before diagnosis.



Time course of development of diabetic nephropathy

The relationship of time from onset of diabetes, the glomerular filtration rate (GFR), and the serum creatinine are shown

Pathogenesis of diabetic nephropathy:

3 lesions:

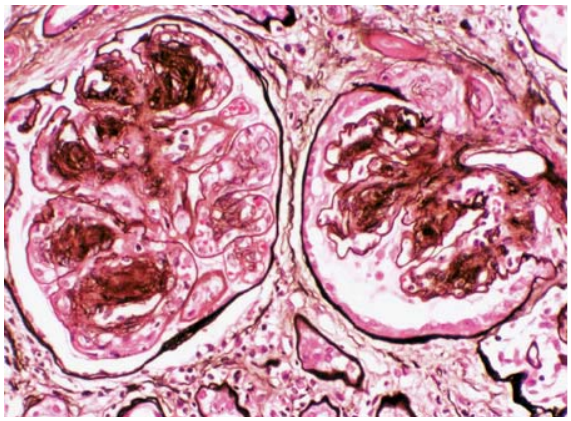
1. Glomerular
2. Vascular
3. Infection (particularly necrotising papillitis)

Glomerular lesions consist of:
i. *Basement membrane thickening*, due to deposition of AGEs in glomerular capillaries. Although the BM is thickened, it is leaky, and allows albumin to filter through. This occurs within a few years of onset of hyperglycaemia.

ii. *Glomerulosclerosis*; AGEs are deposited in the mesangium and the *matrix* expands and the mesangial *cells* proliferate → diffuse or nodular glomerulosclerosis. Because of the expansion of the mesangium, the glomerular capillaries are squashed up at the outer edge of the glomeruli, and this → compression of the efferent arterioles and resultant hypoperfusion of tubules, which derive their blood supply from the efferent arterioles.

The nodular form is characteristic of diabetic nephropathy & is known as the Kimmelsteil-Wilson lesion. (PAS +ve, consisting of mucopolysaccharides, lipids, fibrils & collagen). This lesion is seen in ~35% of diabetic patients.

Vascular lesions
Arteriolosclerosis of both afferent & efferent arterioles due to accelerated atherosclerosis. The arteriolosclerosis of the efferent arterioles is characteristic of diabetic nephropathy.*



- Nodular mesangial expansion (Kimmelstiel-Wilson lesions)
- Prominent glomerular basement membranes
- Arteriolar hyalinosis of both afferent and efferent arterioles

Infection - Necrotising papillitis
This lesion is also characteristic of diabetic nephropathy, & is caused by the combination of ↑ susceptibility to infection as well as tubular & interstitial ischaemia, as discussed above.

(Due to the glycosuria, glucose is absorbed into the tubular cells, where it is converted to glycogen & stored. This does not appear to cause any functional impairment.)

Treatment of early diabetic nephropathy
- Strict BP control: ACE inhibitors angiotensin II blockers → vasodilatation of efferent arteriole → ↓intra-glomerular pressure and better perfusion of tubules.
- Strict glucose level control to limit AGE deposition in basement membrane and mesangium

***Causes of accelerated atherosclerosis in Diabetes Mellitus:**

1. 50% of diabetics have ↑LDL, ↑TG, ↓HDL – due in part to ↓activity of lipoprotein lipase, in part to ↑production because of plentiful supply of FA secondary to lipolysis.
2. Even when lipoprotein levels are normal, they are functionally impaired due to glycosylation, and may be deposited in tissues more readily than normal.
3. Deposition of AGEs in intima of blood vessels and cross linkages between the molecules → entrapment of LDL with deposition of cholesterol to form plaques.
4. ~70% Diabetics are hypertensive → ↑propensity for developing atherosclerosis.

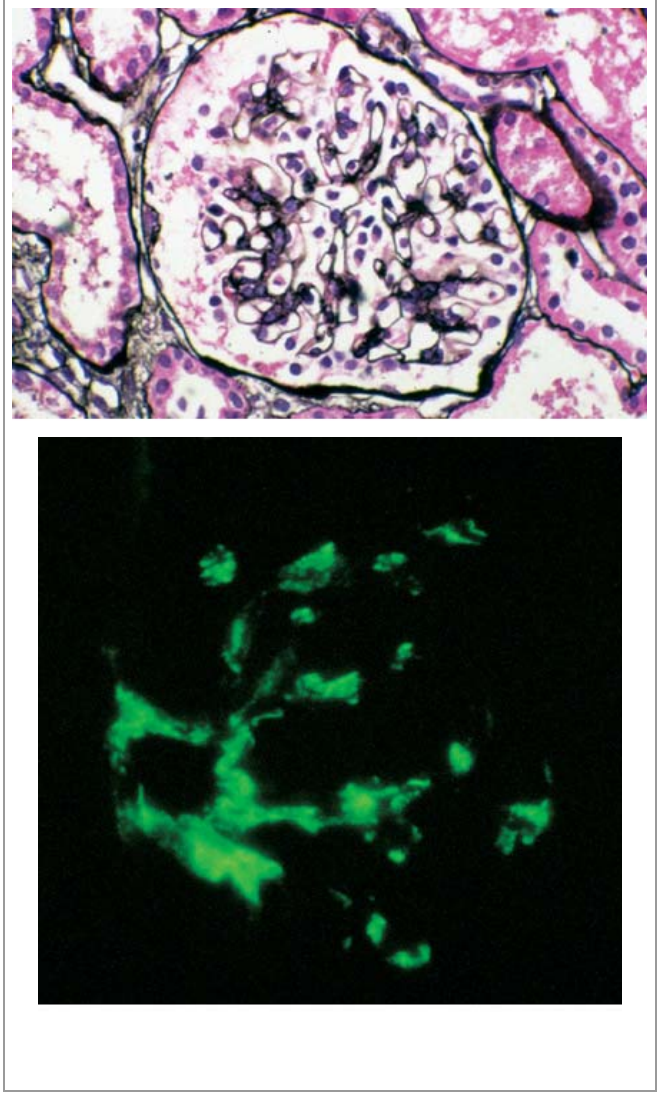
2. Hypertension

Arteriolosclerotic lesions of afferent and efferent arterioles and the glomerular capillary tufts are the most common renal lesions in hypertension and result in progressive ↓ in GFR and tubular dysfunction.
Proteinuria and microscopic haematuria occur because of glomerular lesions.
The characteristic pathology is in the afferent arterioles, which have thickened walls due to deposition of homogeneous eosinophilic material (hyaline arteriolosclerosis).
Narrowing of vascular lumina results with consequent ischaemic injury to glomeruli and tubules.

3. Chronic Glomerulonephritis

IgA Nephropathy

This is the most common form of glomerulonephritis worldwide, being the culprit in up to 40% of cases. The pathogenesis is incompletely understood. IgA production by plasma cells is increased and glycosylation of IgA may occur with impairment of IgA clearance.



IgA is deposited in glomeruli (top) and is evident on immunofluorescence (bottom) of renal biopsy specimens

Most cases are idiopathic
Some are associated with Henoch-Schonlein purpure (considered to be part of the same disease process)
Occasionally found in association with systemic diseases such as:

- Chronic liver disease
- Crohn's disease
- Ankylosing spondylitis

Presentation

Typically presents 24 – 48 hours after an URTI or gastrointestinal infection, vaccination or strenuous exercise, with gross haematuria. The condition tends to smoulder for decades with intermittent exacerbations of haematuria and gradually declining renal function. Up to 50% of patients develop endstage renal disease after 20 years.

Treatment

Observation
ACE inhibitors
Steroids

Summary of features of chronic kidney disease

History and Presentation

History of chronic GN, DM, HT
Onset is insidious. As GFR progressively↓, urea and creatinine levels in the blood ↑accordingly.
Renal excretion of creatinine continues at a constant rate of 10 mmol/day
(*Urinary creatinine excretion = GFR x plasma creatinine*; as GFR↓, creatinine plasma level↑ and amount of filtered creatinine remains unchanged)

Early CKD

Symptoms are minimal early on. Tiredness and ↓mental acuity may occur.
In the blood, *sodium and water balance are maintained* as remaining functioning nephrons fail to reabsorb usual amounts of sodium → ↑urinary excretion. (So even though ↓filtration of sodium, ↑excretion → sodium balance)
Tubules lose their concentrating ability, so urine volume is maintained. The SG of the urine approaches that of plasma (1.010) = isosthenuria
Nocturia is typical, as tubules fail to reabsorb water due to ↓concentrating ability, and high solute load → solute diuresis (high levels of urea filtered because high levels in the blood)

Advanced CKD

Symptoms:
Tiredness, anorexia (↑leptin), nausea, vomiting, pruritus
Signs:
◦ Hypertension in >80% ·↑ fluid balance
·↑ renin in some patients
◦ Fluid overload. As number of mal-functioning nephrons ↑ to ≥75%, kidney is unable to excrete sufficient water (and solutes)
◦ Sallow skin, uraemic frost (rarely seen)
◦ Cardiomyopathy secondary to hypertension/IHD → pulmonary oedema /CCF
◦ Pericarditis

Urinalysis

Proteinuria
Broad casts
SG 1.010

Blood Tests

·Similar results to those seen in ARF
·Lipid Screen: ↑TG
Total cholesterol normal
↓ HDL
↑ oxidised LDL
↑ Lp a
↑ Homocysteine

Imaging

Xray:	Renal osteodystrophy
Ultrasound:	Bilateral shrunken kidneys <10cm in length
Doppler	Renal artery stenosis

DIALYSIS – indications in CRF:

- GFR < 10 ml/min
- GFR < 15 ml/min in Diabetic nephropathy
- Uraemic signs & symptoms severe e.g. vomiting, tiredness, pericarditis, pulmonary oedema

ACUTE VS CHRONIC RENAL FAILURE

As the blood chemistry may be indistinguishable between acute and chronic renal failure, and a history may not be available, it may be difficult to decide whether a patient's renal failure is chronic or of more recent onset. Some characteristic features of acute versus chronic renal failure follow.

FINDING	COMMENT
Prior known ↑s-creatinine	Most reliable evidence of CRF
Renal Ultrasound:	
Small kidneys	High association with CRF
Normal/enlarged kidneys	May be associated with ARF and some forms of CRF e.g. PCKD
Oliguria, daily ↑s-creatinine and urea	Probably ARF or ARF superimposed on CRF
Band keratopathy	Probably CRF
No anaemia	Probably ARF or CRF from PCKD
Severe anaemia, ↓calcium, ↑phosphate	Possibly CRF but seen also in ARF
Subperiosteal erosions on Xray	Probably CRF
Symptoms/signs of fatigue, nausea, pruritus, nocturia, hypertension	High association with CRF

CRF = chronic renal failure
ARF = acute renal failure
PCKD = polycystic kidney disease

Laboratory evaluation of urine and blood in the diagnosis of renal failure – a comparison between acute and chronic renal failure

Acute renal failure is suspected when urine output falls or serum urea and creatinine rise, in the setting of an acutely ill patient with any of the predisposing causes.
A progressive daily rise in serum creatinine is diagnostic of ARF. Serum creatinine can increase by as much as 180 μmol/L per day.

The most reliable evidence of chronic renal failure is a known prior ↑in serum creatinine

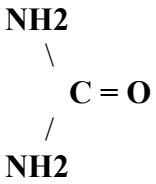
Azotaemia is elevation of urea and creatinine
Uraemia is azotaemia accompanied by clinical signs and symptoms of renal failure.

	Urine Volume	Urine Chemistry	Blood Chem / Haem
Pre-renal Uraemia	50 – 400ml/day	Na <20mmol/L* Urea >250mmol/L U/P osmolality >1.5	↑ Urea ↑ Creatinine
Acute Renal Failure	*Oliguric phase (↓↓GFR)* *(1 - 6wks)* 50 – 400ml/day ********** Recovery phases: *§Diuretic phase (3-7 days)* 3 – 5 L/day *Post diuretic phase (several days)* Urine vol ↓ to 1- 1.5L/day	Na > 40mmol/L ↓Urea < 160mmol/L U/P osmolality < 1.5 *********	↓ Na (dilutional) ↑ K** ↑ Phosphate N/↓ Calcium ↑ Urea ↑ Creatinine ↓ Bicarbonate N/↓Hb***
Chronic Renal Failure	Nocturia Urine vol proportional to intake	↑Urea→high solute load ↑Protein U/P osmolality 1.0 (isosthenuria) *§§ U-osmolality is normally 2.5 – 4x > P- osmolality*	N/↓ Na N/↑ K ↑ Phosphate N/↓ Calcium ↑ Urea, ↑Creatinine ↓ Bicarbonate ↓↓ Hb
Endstage Chronic Renal Failure	↓Urine volume	↓Proteinuria	↓Na ↑K ↑↑ Phosphate ↓↓ Calcium ↑↑ Urea, ↑↑Creatinine ↓↓ Bicarbonate ↓↓ Hb

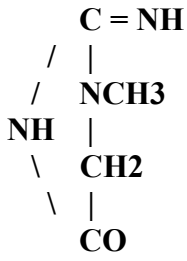
* Aldosterone effect. There is no intrinsic renal damage at this stage, so urea is filtered as usual → high osmolality of the urine
**↑K+ usually secondary to ↓filtration, diuretics/K^+ in diet/blood transfusion/acidosis
***Anaemia develops once 80% renal function has been lost
*§*Diuretic phase of ARF occurs as glomerular function recovers while tubular function lags behind, so filtration occurs but concentrating ability still impaired.
§§ U-osmolality is *usually* 500 – 800 mmol/L (Normal range: 100 – 1000 mmol/L)

Nitrogen-containing substances which we routinely measure and which accumulate in renal failure are:

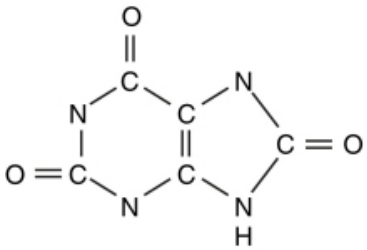
1. **Urea** – derived from NH_3 (= ammonia, the end-product of protein breakdown)



2. **Creatinine** - derived from creatine and creatine phosphate in muscle



3. **Uric Acid** - derived from metabolism of purines - adenine and guanine



Other substances which accumulate in renal failure and which we measure routinely are some of the electrolytes, namely:

Potassium – our daily ingested potassium = ~ 100mmol. Most of this is excreted by the kidney, so in renal failure, hyperkalaemia readily develops.

Phosphate – 90% of phosphate is excreted by the kidneys. ↑PTH levels in response to hypocalcaemia cause further increases in the phosphate level, as osteoclastic activity in bone → calcium and phosphate being released into the circulation.

Magnesium – level increases in renal failure.

Levels of some electrolytes may be normal or reduced:

· **Sodium (**normal) - ↑urinary excretion

· **Calcium** (decreased) due to ↓active Vitamin D
· **Bicarbonate (**decreased) – used up in buffering H^+, which accumulates due to ↓production of NH_3 by the kidneys in renal failure.

Uraemic toxins and atherosclerosis in uraemia

Uraemic toxins

A variety of solutes are retained in renal failure, and may have a toxic effect on the tissues → clinical syndrome of uraemia.

These include:

- **Small molecules** — e.g. urea, which degrades → ammonia + cyanate
- **Larger molecules** "middle molecules" — e.g. β2- microglobulin (one of the MHC proteins)
- **Other solutes:**
  - · protein derivatives (proteins damaged by oxidation or cyanate
    e.g. oxidised LDL
    lipoprotein a
  - · cytokines
  - · homocysteine (derived from methionine)
  - · ADMA (derived from arginine - asymmetric dimethyl arginine)
  - · Ig light chains
  - · Leptin, angiogenin, phosphate, oxalate, indoles, skatoles, hippuric acid*

Atherosclerosis in uraemia

Development of atherosclerosis is accelerated in CRF due to the following:

· ↑Levels of bad things → damage to vessel walls & hyperlipidaemia
· ↓Levels of good things, which normally protect our vessels and promote sensitivity to insulin.
(↓sensitivity to insulin → ↑VLDL)

↑Bad things	↓Good things
ADMA ROS Cyanate (OCN^-) Homocysteine Cytokines ↑Ca:PO_4 product	Nitrous oxide Adiponectin L-carnitine

Bad things

ADMA inhibits nitrous oxide synthase, the enzyme required for NO synthesis in the endothelium; NO is vasoprotective → vasodilatation and promotes sensitivity to insulin

ROS (Reactive oxygen species) - derived from oxygen
e.g. hydrogen peroxide H_2O_2
hydroperoxyl radical HO_2^-

neutrophil activation
↑ ↓
ROS

↑Levels of ROS in CRF due to:
· Dialysis membrane → neutrophil activation → ROS
· Fe++ liberated by RBCs which have shortened lifespan in CRF (abnormal shape, ↓L-carnitine)
· ↓Ingestion of antioxidants (poor appetite in CRF due to ↑leptin)

Cyanate (OCN^-)

$$NH_2 \backslash C = O \rightarrow NH_3 + OCN^- \quad NH_2 /$$

Cyanate damages proteins → accumulation of abnormal proteins, such as lipoprotein a, a very atherogenic type of LDL, in which an extra protein (similar in structure to plasminogen) is bonded to the apo-protein of LDL.

Homocysteine
- · damages vessel walls
- · promotes thrombosis
- · ↓insulin sensitivity

Cytokines produced by activated neutrophils, promote hepatic production of CRP, which damages endothelium

Ca:PO_4 product – as calcium level falls due to ↓active vitamin D, PTH level↑ → osteoclast activation & ↑levels of both calcium and phosphate; when the Ca:PO_4 product reaches a critical level, calcium starts precipitating out and deposition in vessel walls → sclerosis

Good things

Nitrous oxide
- · → vasodilatation
- ·↑sensitivity to insulin

Adiponectin
- · inhibits monocyte adhesion to endothelium
- · anti-inflammatory
- · ↑sensitivity to insulin

L-carnitine
- · required for β-oxidation of fats; absence → ↑VLDL production
- · required for healthy erythropoiesis; absence → ↓red cell survival

*_Leptin_ is produced by adipose tissue, binds to neurones in the hypothalamus (satiety centre) relaying the message that we are satiated

Angiogenin, a protein that binds to endothelial cells, is endocytosed and promotes new vessel formation

Indole, a product of bacterial breakdown of tryptophan in the GIT, gives our faeces its characteristic odour.

Skatole (methylated indole) is also malodorous

Hippuric acid is a peptide derived from the conversion of angiotensin I → II

SIADH

(Syndrome of Inappropriate Secretion of Antidiuretic Hormone)

SIADH is an important cause of hyponatraemia. This syndrome is caused either by inappropriate secretion of ADH from the posterior pituitary gland or by ectopic production of ADH by a tumour. Example: Carcinoma of the Lung

The excessive reabsorption of water in the distal nephron continues in the face of a dilute ECF, the concentration of both sodium and urea in the plasma being predominantly affected (decreased). This will cause the plasma osmolality to fall, as can be seen by the formula:

Plasma Osmolality = 2x Sodium + Urea + Glucose (mmol/L)*

The concentration of the other electrolytes in the plasma is usually unaffected.
The diagnosis is made by comparing plasma osmolality with urine osmolality; in the normal course of events, when plasma osmolality falls, urine osmolality will also fall, as ADH secretion is inhibited by hyponatraemia. (Example: In psychogenic polydipsia)
In SIADH, urine osmolality is inappropriately high (concentrated urine because ↑↑reabsorption of water), in the face of a ↓plasma osmolality.
Diagnosis confirmed when U- osmolality > P- osmolality or U- osmolality > 200 mmol/L, in the face of ↓P- osmolality.

Common causes

Drugs: tricyclic antidepressants, carbamazepine, phenothiazines, omeprazole, chlorpropamide, vincristine, vinblastine, cyclophosphamide, clofibrate, haloperidol, angiotensin converting enzyme inhibitors, narcotics, nicotine, monoamine oxidase inhibitors, SSRIs, and many others

Post-operative stress caused by surgery, use of a mechanical ventilator, or anaesthetic agents

CNS disturbances due to: infections (meningitis, brain abscess)
stroke
trauma
neurosurgery

Pulmonary disorders: pneumonia, tuberculosis, emphysema, status asthmaticus

Rare causes

Malignant disease
- **Neoplasm** in the lung (most commonly small cell carcinoma), duodenum, pancreas, olfactory neuroblastoma, bladder, prostate, thymus, or brain
- **Lymphoma**
- **Leukaemia**
- **Mesothelioma**
- **Ewing's sarcoma**

Psychoses

Hormone administration: vasopressin or oxytocin

**Normal P-Osmolality: 275 – 295 mmol/L*

Urine Osmolality

I. **Normal**
   A. 50-1200 mOsm/kg (Ave 500 – 800mmol/L)

II. **Increased**
   A. Syndrome Inappropriate ADH Secretion (SIADH)
   B. Dehydration
   C. Glycosuria
   D. Adrenal Insufficiency
   E. High protein diet

III. **Decreased**
   A. Diabetes Insipidus
   B. Excessive hydration (oral or intravenous)
   C. Acute renal insufficiency

In SIADH, urine osmolality should be low, because plasma osmolality is ↓; however it remains inappropriately high. Diagnostic level = >200 mmol/L

In pre-renal uraemia, urea is filtered as usual, and aldosterone and ADH levels increase due to fall in BP → concentrated urine, with ↓Na level: urine osmolality ↑.

In intrinsic renal failure, urea filtration ↓ and concentrating ability of kidneys is impaired → ↓osmolality

Osmolality of a solution = 2 x sodium content + urea + glucose (mmol)

Nephrotic Syndrome

Definition:
- Proteinuria of ≥3.0 g/day
- Hypoalbuminaemia
- Oedema
- Hyperlipidaemia

Consequences:

Proteinuria

Damage to the glomerular basement membrane results initially in leakage of albumin into the tubules → hypoalbuminaemia. As the condition progresses, higher molecular weight proteins are lost in the urine and the urinary protein losses can be massive.

Hypercoagulable state

Nephrotic patients often have a hypercoagulable state, and are predisposed to DVT, pulmonary embolism and renal vein thrombosis. There is loss of urokinase and anti-thrombin 3 (ATT) in the urine, and ↑levels of factor VIII, fibrinogen and platelets in the blood.

Hypogammaglobulinaemia

These patients are also prone to infections, as they develop hypogammaglobulinaemia due to Immunoglobulin loss in the urine.

Oedema is often the presenting feature and is due in part to ↓oncotic pressure due to hypoproteinaemia. Some patients are resistant to the effects of atrial natriuretic peptide, and reabsorb inappropriate amounts of sodium and water in the tubules, and may become oedematous even when the serum albumin is not very low.

Hyperlipidaemia is contributed to by both ↑TG and total cholesterol, mainly due to ↑LDL-cholesterol. It is hypothesised that hepatic lipoprotein and albumin production are linked, and the ↑hepatic synthesis of albumin in response to ↓plasma levels, results also in ↑hepatic synthesis of lipoproteins.

Another hypothesis is that a protein important in regulation of lipoprotein synthesis is lost in the urine in this syndrome, resulting in disordered hepatic production of lipoproteins.

There is ↑hepatic production of cholesterol and manufacture of LDL de novo in the liver occurs. ↓Activity of LCAT and also of lipoprotein lipase (LPL) is evident.

Loss of heparan sulphate in the urine means that the attachment of lipoprotein lipase to the endothelium is impaired, and the free LPL is therefore easily lost in the urine. ↑Circulation time of VLDL results, with ↑TG level.

↑Levels of Lp(a) is also often found and this contributes to the tremendous hyperlipidaemia which is a hallmark of this condition.

Causes:

*Glomerulonephritis	Membranous, minimal change, focal segmental, proliferative etc
Systemic diseases	*Diabetes, SLE, *Amyloidosis, Sarcoidosis, vasculitic-immunologic diseases e.g. polyarteritis nodosa
Infections	Bacterial (streptococcal, syphilis, SBE) Viral (Hepatitis, HIV, infectious mononucleosis, CMV) Parasitic (malaria, toxoplasmosis, schistosomiasis, filariasis)
Drugs	Gold, mercury, NSAIDs, lithium, heroin
Neoplasms	Hodgkin's disease, solid tumours
Hereditary	Alport's syndrome, Sickle cell anaemia, familial nephrotic syndrome
Other	Pregnancy, massive obesity, renal artery stenosis, transplant rejection

***Most common**

ELECTROLYTES

Potassium

Hyperkalaemia	Hypokalaemia
Metabolic acidosis	Metabolic alkalosis
Renal failure	D&V / Laxative abuse
Addison's disease	Steroid Rx / Conn's syndrome
Diuretics e.g. ACE inhibitors	Diuretics e.g. Frusemide
Rhabdomyolysis	Liquorice
Burns	Villous adenoma
Massive blood transfusion	

◦Acute metabolic acidosis →↓function of Na:K pump→↓IC K+ and ↑ECF K+; in the kidney, because the concentration in the tubular cell is↓, there is reduced diffusion → the tubular lumen → accumulation of K+ in the body.
◦Renal failure means that amount of K filtered is ↓↓ and so accumulates in the ECF
◦In rhabdomyolysis, K+ is released as the cells lyse
◦The mechanism by which metabolic alkalosis→ ↓K+ is incompletely understood; however, there is an influx of K+ into the cells, including the tubular cells, and ↑diffusion across the tubular membrane into the lumen, resulting in ↑loss in the urine.
◦The ↑urine flow rate resulting from a diuretic stimulates K+ secretion →lumen of the DCT and loop of Henle.
◦Liquorice has an aldosterone-like effect

ECG changes of hyperkalaemia K+ >5.5 mmol/L
(Usually *asymptomatic* until ECG changes occur):
Short QT interval
Tall T waves
ST elevation
Arrhythmias – sinus bradycardia, nodal/ventricular arrhythmias
Widened QRS
P wave disappears
Finally, QRS → sine wave and asystole / ventricular fibrillation

ECG changes of Hypokalaemia K+ <3.5 mmol/L	Signs and Symptoms
1st/2nd/3rddegree heart block	Muscle weakness, cramps, fasciculations
T wave flattening	Paralytic ileus
ST depression	↓Ventilation
Prominent U waves	↓BP
APBs/VPBs	Rhabdomyolysis
Atrial/ventricular tachyarrhythmias	Nephrogenic diabetes insipidus
Potentiation of adverse effects of Digoxin	(tubules damaged & cannot respond to ADH)

Normal renal handling of potassium

We daily ingest 100mmol K+, the majority of which is excreted by the kidneys

Should we be hypo- or hyperkalaemic, K+ may be reabsorbed from the filtrate as it passes through the DCT and collecting duct or secreted into the filtrate here in greater amounts to restore potassium balance..

Sodium

Hypernatraemia		Hyponatraemia	
↑Na	Conn's syndrome	↓↓Na:↓H_2O	•D&V
↓H_2O	•Dehydration		•Diuretics
	•Diabetes Insipidus		•DM→osmotic diuresis
			•Addison's Disease
		Normal Na:↑H_2O	•↑ADH e.g. Ca bronchus (SIADH)
			•Psychogenic polydipsia
		↑Na: ↑↑H_2O	•cardiac failure
			•renal failure
			•liver failure
			•nephrotic syndrome

Hyponatraemia is the commonest electrolyte abnormality in the elderly and is associated with a high mortality, because of the diseases associated with it.

Renal handling of sodium and water

Renal Na+ excretion = amount filtered — amount reabsorbed
65% of filtered electrolytes (including Na+) are reabsorbed in the PCT. Here Na+ binds to a carrier protein and enters the tubular cell, at the same time as H+ leaves the cell → tubular lumen, the energy being derived from a diffusion gradient for Na+ having been created by the Na:K ATP-ase pump, situated in the contralateral wall of the tubular cell.
As the filtrate enters the Loop of Henle, permeability to water ↑↑ and permeability to electrolytes ↓.Thus the filtrate becomes concentrated here.
As the filtrate passes into the ascending limb, permeability to water↓↓ and this is the status quo till the distal end of DCT is reached.
Once the filtrate reaches the thick part of the ascending limb of the Loop of Henle, active reabsorption of electrolytes takes place and continues till it reaches distal DCT.
In distal DCT and collecting ducts, ADH exerts its effect and promotes reabsorption of water. The level of ADH is dependent on the osmolality of the blood.
It is in this area of the nephron that aldosterone has its effect too, enhancing Na+ and water reabsorption and promoting K+ excretion. The stimulus for aldosterone secretion (via renin) is a fall in BP detected by the JGA cells as well as a decreased level of sodium in the filtrate; hyperkalaemia also stimulates aldosterone release.

Effective osmolality of a solution is ∞ to its Na content.

Normal plasma osmolality = 275 – 295 mmol/L

Calcium

Hypercalcaemia	Hypocalcaemia
Common:	Parathyroidectomy
Hyperparathyroidism (adenoma)	1º Hypoparathyroidism
Malignancy	Vit D deficiency (CRF/↓sunlight)
Rare:	Acute pancreatitis
Sarcoidosis	Pseudohypoparathyroidism
Paget's disease	Severe alkalosis

◦ The hypercalcaemia of malignancy is caused by a PTH-related peptide
◦ Sarcoidosis →↑Vit D activity. (Also ↑ACE levels)
◦ Paget's disease →↑ALP and osteoclastic activity in bone.
◦ Calcium is chelated by products of lipolysis occasioned by release of pancreatic lipase in acute pancreatitis
◦ In pseudohypoparathyroidism, there is ↓responsiveness to PTH

Calcium
41% calcium is bound to plasma proteins
9% is bound to citrate and other anions
50% occurs as free ionised calcium

Hypercalcaemia
Is frequently asymptomatic

GIT symptoms	Renal symptoms	CNS symptoms
Constipation	Polyuria	Emotional lability
Anorexia, nausea, vomiting	Polydipsia	Confusion
Abdominal pain	Nocturia	Delirium
Ileus	Renal calculi/nephrocalcinosis	Psychosis
Peptic ulcer disease		Stupor/coma
Pancreatitis		

Muscle weakness

ECG: shortened QT interval

Hypocalcaemia
Is frequently asymptomatic

Neuromuscular irritability	CNS symptoms	Cataracts
Muscle cramps	Depression	Chvostek's sign
Tetany	Dementia	Trousseau's sign
Laryngospasm	Psychosis	
Convulsions	Papilloedema	

ECG: prolonged QT interval

Phosphate

↑Phosphate levels	↓Phosphate levels
Renal Failure	Critical illness
Massive cell necrosis especially ischaemic bowel (intracellular anion)	Alcoholism
	Diuretics
Metabolic acidosis	Metabolic alkalosis
	1˚ Hyperparathyroidism

◦↓Phosphate levels post DKA and severe burns
◦10% patients admitted for alcohol-related illness have ↓phosphate levels

Phosphate *20% is intracellular (the main IC anion). Binds reversibly to many compounds such as. ATP, ADP, phosphocreatine and is important in nucleic acid synthesis*
80% is in bone bound to calcium
(Phosphorus is present in many foods, so dietary deficiency is very rare.)

Magnesium

↑Mg levels	↓Mg levels
Renal failure	Alcoholism
	1˚ Hyperparathyroidism
	Diuretics
	Diarrhoea

◦Patients in renal failure who ingest Mg-containing drugs (e.g. antacids) develop ↑Mg levels
◦Patients who are alcohol dependent, develop ↓Mg levels due to poor intake and ↑renal excretion

Magnesium *Functions as a catalyst in reactions involved in carbohydrate metabolism*
65% occurs in bone
35% is intracellular

Chloride

↑ Chloride	↓ Chloride
Normal anion gap acidosis:	Metabolic alkalosis
(↓Bicarb = ↑Chloride)	(↑Bicarb = ↓Chloride)
Iatrogenic - ↑volumes NaCl administered iv	Vomiting
	Diarrhoea

Chloride ion is very obliging – he likes to please, so:

When bicarb goes down, chloride goes up (to maintain electrical neutrality)

When bicarb goes up, chloride goes down.

When acidosis is present: **↑H+ ↑K+ ↑Cl^- ↑PO_4 (↓HCO_3^-)**

When alkalosis is present: **↓H+ ↓K+ ↓Cl^- ↓PO_4 (↑HCO_3^-)**

Parathyroid Hormone, Vitamin D and Calcitonin.

PTH

1. Mobilises calcium and phosphate from bone, by ↑osteoclast activity
2. ↑Renal reabsorption of calcium, promotes renal excretion of phosphate
3. Stimulates 1 - hydroxylation of 25 - OH Vitamin D by the kidney

PTH has no direct effect on GIT absorption of calcium

Vitamin D

1. ↑GIT absorption of calcium and phosphate by stimulating formation of a carrier protein – major effect
2. ↑Renal reabsorption of calcium and phosphate – minor effect
3. In large amounts, facilitates the action of PTH on bone resorption
4. In smaller amounts, promotes bone mineralisation

Calcitriol is a synonym for 1,25 - hydroxyVitamin D_3

We derive most of our Vitamin D supply by the action of sunlight on 7 -dehydrocholesterol in the skin. A small amount is obtained from our diet – egg yolk, green veg (spinach, cabbage) and oily fish.

Sunlight ☼ liver kidney

↓ ↓ ↓

7 – dehydrocholesterol → cholecalciferol → 25-OH VitD_3 → 1,25-OH VitD_3

The α -1 Hydroxylase enzyme is inhibited by ↑PO_4, stimulated by ↓ PO_4

Calcitonin

Is a hormone produced by the parafollicular "C" cells of the thyroid gland. Its effects are opposite to those of PTH