The Henderson-Hasselbalch equation for the carbonic acid/bicarbonate buffer system (modified form):

\[ \text{pH} = \text{pKa}' + \log \frac{[\text{HCO}_3^-]}{S \times P_{\text{CO}_2}} \]

1. How is this equation derived? What does S stand for?

For any acid, the concentration of the acid relative to its dissociated ions is defined by the dissociation constant (K')

\[ K' = \frac{[H^+] \times [\text{HCO}_3^-]}{[\text{H}_2\text{CO}_3]} \]

In a solution of H₂CO₃, the amount of free hydrogen ions is equal to:

\[ H^+ = K' \times \frac{[\text{H}_2\text{CO}_3]}{[\text{HCO}_3^-]} \] (Henderson equation)

[H₂CO₃] in solution can’t be measured as it dissociates rapidly – however, the CO₂ dissolved in blood is directly proportional to the amount of undissociated H₂CO₃:

\[ H^+ = K \times \frac{[\text{CO}_2]}{[\text{HCO}_3^-]} \]

The solubility coefficient for CO₂ is 0.03mmol/mmHg at body temperature (0.03 millimole of H₂CO₃ is present for each mmHg P₇CO₂ measured at 37°C):

\[ H^+ = K \times \frac{(0.03 \times P_{\text{CO}_2})}{[\text{HCO}_3^-]} \]

Given that pK = -log K, we can express the [H⁺] in pH units by taking the negative logarithm of the equation:

\[ \text{pH} = \text{pK} - \log \frac{(0.03 \times P_{\text{CO}_2})}{[\text{HCO}_3^-]} \]

Rearranging, and given that pK is 6.1 for the bicarbonate system we have:

\[ \text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{(0.03 \times P_{\text{CO}_2})} \]

This is the Henderson-Hasselbalch equation – S is the solubility coefficient for CO₂ under physiological conditions (0.231 in mmol/kPa, 0.03 in mmol/mmHg).

2. What organs regulate the arterial blood pH to 7.4 ± 0.04 at sea level?

Along with the chemical acid-base buffer systems of the body fluids, the lungs and kidneys also act to regulate blood pH. The respiratory centre regulates removal of CO₂ from extracellular fluid, while the kidneys can secrete acid or alkaline urine as necessary to eliminate base/acid excess.

\[ \text{pH} = 6.1 + \log \frac{24}{(0.03 \times 40)} \]
\[ \text{pH} = 6.1 + \log 20 \]
\[ \text{pH} = 7.4 \]

3. Why is the Henderson-Hasselbalch equation useful in understanding acid-base balance?

The Henderson-Hasselbalch equation allows us to calculate the pH of a solution if the molar concentration of bicarbonate ion and the P₇CO₂ are known – it also provides insight into the physiological control of acid-base balance by the lungs (CO₂/P₇CO₂) and kidneys (HCO₃⁻).

\[ H^+ = K_{a1} \frac{[\text{HA}_1]}{[A_1]} = K_{a2} \frac{[\text{HA}_2]}{[A_2]} = K_{a3} \frac{[\text{HA}_3]}{[A_3]} \text{ etc.} \]

Buffers in the body are critical in preventing excessive falls in plasma pH following the addition of strong acid.
1. What are the buffers involved, and what fluid compartments are they found in?

2. What are the relative contributions of these buffers to buffering the infused acid?

Bicarbonate buffer system, consisting of a weak acid (H$_2$CO$_3$) and a bicarbonate salt (such as NaHCO$_3$). This is the most important extracellular buffer as two elements of the system are regulated by the kidneys and lungs (HCO$_3^-$ and CO$_2$).

Phosphate buffer system, consisting of H$_2$PO$_4^-$ and HPO$_4^{2-}$ – these act to trade strong acids/bases for weak acids/bases. This system plays a major role in buffering renal tubular fluid and intracellular fluids.

Proteins (e.g. haemoglobin) also form an important intracellular buffer system, mainly due to their high concentrations (particularly within cells) but also as their pKs are typically close to 7.4.

Note that diffusion of the elements of the bicarbonate buffer system (e.g. CO$_2$ across all cell membranes) causes the pH in intracellular fluids to change when there are changes in extracellular pH.

3. The normal ratio of $\frac{[HCO_3^-]}{S \times P_{CO_2}}$ is 20/1. In five animals given a HCl infusion the ratio was reduced to a mean of 10/1. What was the mean pH?

From Henderson-Hasselbalch equation:

$$pH = 6.1 + \log \left( \frac{HCO_3^-}{0.03 \times P_{CO_2}} \right)$$

$$pH = 6.1 + \log 10$$

$$pH = 6.1 + 1$$

$$pH = 7.1$$

4. Why had the molar [CO$_2$] fallen? What would have happened to the pH if it had remained at the normal value of 1.2mmolL$^{-1}$?

When a strong acid is added to a bicarbonate buffer solution, the increased hydrogen ions released from the acid are buffered by HCO$_3^-$:

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

The increased CO$_2$ production greatly stimulates respiration (via carotid bodies) and removes it from the plasma compartment. If the [CO$_2$] had remained at 1.2mmolL$^{-1}$:

$$pH = 6.1 + \log \left( \frac{HCO_3^-}{0.03 \times P_{CO_2}} \right)$$

$$pH = 6.1 + \log \frac{7 \text{ mmolL}^{-1}}{1.2 \text{ mmolL}^{-1}}$$

$$pH = 6.1 + \log 5.83$$

$$pH = 6.1 + 0.7659$$

$$pH = 6.86$$, which is acidosis

After a period of ventilation with pure oxygen, apnoea can be sustained for some time without hypoxia occurring. However, carbon dioxide accumulates and the arterial $P_{CO_2}$ rises at a rate of 3-6mmHg/min. Under these conditions:

1. What happens to the plasma [HCO$_3^-$]? Plasma [HCO$_3^-$] increases to compensate for rising CO$_2$ levels:

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

2. How is the additional H$^+$ from the carbonic acid buffered?

Increased [H$^+$] stimulates alveolar ventilation due to the lowered pH. The amount of oxygen added to the blood increases, and the $P_{O_2}$ in the blood also rises. This leads to a decrease in the $P_{CO_2}$ in extracellular fluids and a reduction in hydrogen ion concentration towards normal.

Major buffers of H$^+$ in this situation are haemoglobin (also proteins in tissue cells and bone) and renal excretion of H$^+$ after 2-5 days.
3. How rapidly does this occur?
Respiratory regulation of acid-base balance is a physiological buffer system as it acts rapidly (3-12 minutes) and keeps [H+] from changing too much until the much more slowly responding kidneys can eliminate the imbalance.

4. What happens to the pH?
The respiratory system for controlling [H+] has an effectiveness of 50-75%, which translates to a feedback gain of 1 to 3. Hence if pH were to fall from 7.4 to 7.0, the respiratory system would be capable of returning it to 7.2 to 7.3.

The variables of the Henderson-Hasselbalch equation can be plotted graphically in a variety of ways. Two forms are the pH/log $P_{CO_2}$ diagram and the Siggaard-Andersen alignment nomogram (SAAN).

1. In the pH/log $P_{CO_2}$ diagram what does the “normal buffer line” represent?
The normal buffer line represents the line for constant bicarbonate concentration of 25 mmol/L. The point where it intersects $P_{CO_2}$ of 40 mmHg and pH 7.4 is approximately the centre of the ‘normal’ range.

2. Why does its slope change depending on the haemoglobin concentration?
The haemoglobin concentration alters the ability of blood to carry oxygen, and this has effects on $P_{O_2}$ and subsequently $P_{CO_2}$. For example, a decreased level of Hb reduces the amount of $O_2$ added to the blood, $P_{O_2}$ and $P_{CO_2}$ – hence the pH will change less rapidly if $P_{CO_2}$ is changed.

3. How are base excess (BE) and base deficit (BD) defined?
Base excess is expressed as milliequivalents per litre above or below the normal buffer-base range. It is defined as:
   a. The quantity of strong acid which has to be added to a litre of fully saturated blood at 37°C to bring its pH to 7.4 when $P_{CO_2}$ is 40 mmHg
   b. Actual total buffer-base – normal total buffer-base

Base deficit is a negative base excess and can be used to estimate how much NaHCO$_3$ to give to a patient:
   Dose (mEq) = 0.3 x Wt (kg) x BE (mEq/L)

4. Can BE and BD be estimated in a patient?
Clinically BE can be estimated from blood, but is not always useful as
   a. Acid-base disturbances are not usually static
   b. BE is a measurement on blood, and may not apply accurately to extracellular fluid and does not reflect directly intracellular changes
   c. There may be differences in severity of pH changes in various body compartments

5. Using the SAAN derive the missing values or answer the questions:
   a. $P_{CO_2} = 40mmHg$, $pH = 7.4$  
      $[HCO_3^-] = 24.5mmolL^{-1}$
      BE$_{ECF} = 0$
   b. $[HCO_3^-] = 24mmolL^{-1}$, $pH = 7.2$
      $P_{CO_2} = 63mmHg$
   c. $P_{CO_2} = 40mmHg$, $pH = 7.5$, $[HCO_3^-] = 25.5mmolL^{-1}$ – is this possible?
      Not possible
   d. $P_{CO_2} = 60mmHg$, $pH = 7.25$, $[HCO_3^-] = 25.5mmolL^{-1}$, BE$_{ECF} = -1mmolL^{-1}$
      CO$_2$ = 27mmolL$^{-1}$, Hb = 0.4g/100mL
      CO$_2$ retention – pH is acidic (respiratory acidosis)
   e. $P_{CO_2} = 40mmHg$, $pH = 7.3$, $[HCO_3^-] = 19mmolL^{-1}$, BE$_{ECF} = -6mmolL^{-1}$
      CO$_2$ = 20mmolL$^{-1}$, Hb = 0g/100mL
      Non-volatile acid – metabolic acidosis

Note - -aemia = blood sample, -osis = process (may be compensated)
Examples of the four types of simple (primary) disturbance are given in the table.

1. Name the types and explain which line of data would be consistent with each type

2. No compensation has occurred in any example. What does this mean and what would be an appropriate compensatory response in each of the simple disorders? Compensation refers to physiological mechanisms that attempt to correct disturbed pH towards normal range – note that this does not result in overcorrection of pH.

Respiratory acidosis (c) is due primarily to an increase in $P_{CO_2}$ ($\Rightarrow H^+$ secretion). The compensatory response is an increase in plasma $HCO_3^-$, caused by addition of new bicarbonate to the extracellular fluid by the kidneys.

Respiratory alkalosis (a) is due to decreased plasma $P_{CO_2}$ (hyperventilation) that leads to a decrease in the rate of $H^+$ secretion by renal tubules. The compensatory response is a reduction in plasma $HCO_3^-$ concentration mediated by increased renal excretion.

Metabolic acidosis (b) is due to a fall in $HCO_3^-$ and ECF without a change in $P_{CO_2}$ ($\Rightarrow$ excess $H^+$ due to decreased $HCO_3^-$ filtration). Compensations include increased ventilation (reduces $P_{CO_2}$) and renal $H^+$ excretion, which helps minimise the initial fall in ECF $HCO_3^-$.  

Metabolic alkalosis (d) is due to a rise in the ECF $HCO_3^-$ concentration without a change in $P_{CO_2}$. This is compensated by a reduction in ventilation (increased $P_{CO_2}$) and increased renal $HCO_3^-$ excretion, which helps compensate the initial rise in ECF $HCO_3^-$. 

3. How are simple disturbances different from mixed ones? What combinations of disturbances can possibly occur in mixed disorders?

Acid-base disorders not accompanied by proper compensatory responses are referred to as ‘mixed’ – there are 2-3 underlying causes for the disturbance. If there is extreme acidosis or alkalosis, it is possible that multiple disorders are additive – similarly, mild acidosis or alkalosis could be due to multiple disorders cancelling out.

1. Explain why time courses of respiratory compensation and renal excretion (base/acid) differ

2. What are the mechanisms involved in each of these processes?

Respiratory compensation occurs rapidly because of the sensitivity of peripheral chemoreceptors to blood pH. Control mechanisms respond by hyperventilation ($\Rightarrow$ decreased $P_{CO_2}$) or hypoventilation ($\Rightarrow$ increased $P_{CO_2}$). Central chemoreceptors cannot sense blood pH, and only see changes in $P_{CO_2}$ – hence they tend to inhibit respiratory compensation.

Renal compensation is established within 24 hours, and is maximally effective by 4-5 days. The kidneys compensate for decreased pH by excreting acids (HCl, NH$_4$Cl) and retaining bases (NaHCO$_3$), and compensate for increased pH by excreting base (KHCO$_3$) and retaining acids (HCl).

This is inherently slower than respiratory compensation because the kidney only receives 25% of cardiac output (so it sees less blood) and it is not a neurogenic pathway. Renal acid excretion also requires synthesis of enzymes and substrates which may take some time.
3. Are there limitations on the capacity of the respiratory and renal systems to compensate for simple disorders? If so, what is the cause of these limitations?

With all except minor degrees of acidaemia and alkalaemia, compensatory mechanisms are unable to restore plasma pH to normal values. This is due to the inherent limits in the chemical and neural control systems of respiration and renal tubular secretory and absorptive capacity.

The change in ventilation produced by acidaemia or alkalaemia is proportional to the extent of the change in pH. Hence as the ventilatory effect on arterial $P_{CO_2}$ moves the pH back towards normal, the error signal decreases and prevents an overshoot or overcompensation.

Similarly in the kidney the stimulus for $H^+$ secretion by tubular cells reflects their intracellular pH changes. As the compensation returns extracellular pH toward normal, intracellular pH will also normally be modified in the direction of reducing $H^+$ secretion.

Using the Siggaard-Andersen alignment nomogram, acid-base chart and the table of ‘expected’ values analyse the following data and answer the following questions:

1. $pH_a = 7.33$, $P_{CO_2} = 71$mmHg (9.46kPa)
   $[HCO_3^-] = 37$mmolL$^{-1}$, $BE_{ECF} = 10.1$
   The principle abnormality is a severe respiratory acidaemia, with complete renal compensation (metabolic alkalaemia). This is typical of chronic respiratory disease.

2. $pH_a = 6.96$, $P_{CO_2} = 21$mmHg (2.8kPa)
   $[HCO_3^-] = 4.5$mmolL$^{-1}$, $BE_{ECF} = -25.5$
   The principle abnormality is a severe metabolic acidaemia with marked respiratory alkalaemia. This is typical of a partially (fully?) compensated metabolic disturbance.

3. $pH_a = 7.18$, $P_{CO_2} = 70$mmHg (9.33kPa)
   $[HCO_3^-] = 25.5$mmolL$^{-1}$, $BE_{ECF} = -2.2$
   The principle abnormality is a severe respiratory acidaemia with no metabolic acidaemia. It is characteristic of an uncompensated acute respiratory acidosis.

4. $pH_a = 7.55$, $P_{CO_2} = 60$mmHg (8.0kPa)
   $[HCO_3^-] = 53$mmolL$^{-1}$, $BE_{ECF} = 25.8$
   The main abnormality is a severe metabolic alkalaemia with a marked respiratory acidaemia. This is typical of a compensated metabolic alkalaosis.

5. $pH_a = 7.47$, $P_{CO_2} = 20$mmHg (2.6kPa)
   $[HCO_3^-] = 14.5$mmolL$^{-1}$, $BE_{ECF} = -8.5$
   There is a marked respiratory alkalaemia and a moderate metabolic acidaemia. This is typical in prolonged hyperventilation – i.e. respiratory alkalaosis with renal compensation.

### Acid-Base Physiology 3

1. What is the equation that expresses the relationship between alveolar ventilation and arterial $P_{CO_2}$?
   
   $PA_{CO_2} = \frac{V_{CO_2}}{V_a} \times K$ (where $K$ is a constant) and as $PA_{CO_2} \approx P_{CO_2}$
   
   $P_{CO_2} = \frac{V_{CO_2}}{V_a} \times K$

2. Write the alveolar air equation. How can this equation help analyse acid-base problems?
   
   $PA_{O_2} = P_{O_2} - \frac{PA_{CO_2}}{R} + F$
   
   where $R$ is the respiratory exchange ratio depending on diet (1.0, 0.8 on a mixed diet) and $F$ is a correction factor (1-3mmHg during air breathing).

   This equation enables the alveolar – arterial $P_{O_2}$ gradient to be estimated. If this is abnormal
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(>12mmHg in young adults breathing air at sea level, or >25mm Hg in the healthy elderly) indicates lung problems that may not be immediately obvious from the history or blood gas data.

3. **What is meant by the term anion gap?**
The anion gap is the difference between the sums of the cations [Na⁺] and [K⁺], and the sum of the anions [Cl⁻] and [HCO₃⁻] when all concentrations are expressed as mEq/L.

Some types of metabolic acidosis are associated with accumulation of unmeasured organic anions and a fall in [HCO₃⁻] as a result of buffering, while [Cl⁻] remains unchanged, as is the anion gap. Hence metabolic acidoses can be classified according to the presence/absence of an abnormal anion gap, which may be useful in making a diagnosis on the mechanism or cause of the disturbance.

4. **What is the relationship between changes in plasma pH and the plasma potassium concentration?**
Changes in extracellular pH have effects on plasma [K⁺] particularly in cases of metabolic acidosis due to excess of mineral acid (e.g. renal failure, diarhoea).

In these cases, >60% of excess H⁺ is buffered in cells and K⁺ and Na⁺ enter plasma to maintain electroneutrality. This results in a variable increase for both cationic concentrations, but is only significant for plasma [K⁺] which increases 0.2-1.7mmol/L for each 0.1pH unit fall.

This relationship is much less predictable with organic acidosis (lactic acidosis, ketoacidosis), and changes in plasma [K⁺] with metabolic alkalosis and respiratory disorders are usually much less prominent.

**Case studies:**

1. A 51-year-old, obese man was admitted during a severe episode of bronchial asthma. 100% O₂ by mask was given and the appropriate drug therapy for asthma was instituted. Arterial blood gas values taken at that time, and subsequently, are summarised in the table (see handout). Note that in the interval between the first and second blood samples he was given 200mmol of NaHCO₃ intravenously. He was breathing spontaneously throughout.

0300hrs – respiratory acidosis with metabolic acidosis, probably due to tissue hypoxia and lactic acidosis though this isn’t definitive (see arterial PO₂, FIO₂). Calculated PAO₂ at FIO₂ 1.0 would be 554mmHg and the A-a PO₂ difference around 464mmHg – this probably reflects ventilation/perfusion mismatch and venous admixture in the lungs.

0430hrs – respiratory acidosis reduced (arterial PCO₂ is lower) but there is a metabolic acidosis as well (iatrogenic) resulting in a normal pH. PAO₂ is now 650mmHg and the A-a PO₂ difference around 464mmHg – this probably reflects ventilation/perfusion mismatch and venous admixture in the lungs.

0800 – acid-base status is essentially normal with slight elevation of PCO₂. PAO₂ is 655mmHg, and A-a PO₂ 407mmHg. Note that there are difficulties in achieving 100% O₂ when breathing through a mask unless there are absolutely no leaks.

2. A 28-year-old male was admitted to hospital in coma thought to result from an overdose of tricyclic antidepressant. He had been unconscious for some hours before admission during which time he had had several epileptic seizures. No significant circulatory or respiratory impairment was found. An intravenous infusion of 0.9% NaCl was started and oxygen supplementation by mask begun.

On admission – acidaemia resulting from metabolic acidosis (lactic acid) with substantial but incomplete respiratory compensation (full compensation would be an arterial PCO₂ of 14-20mmHg). Plasma [K⁺] normal, PAO₂ around 256mmHg, A-a PO₂ around 111mmHg.

30 minutes later – acidaemia is now considerably worse, and respiratory compensation is much less than admission (possibly impaired ventilation). Plasma [K⁺] is beginning to fall.
2 hours after admission – a metabolic alkalaemia from the infused bicarbonate is now evident, but oxygenation and ventilation are adequate. Potassium is continuing to fall – the speed of the change suggests it has been translocated into cells (in response to the alkalaemia). Lactate is falling, but still at abnormal levels.

4, 8 and 24 hours after admission – acid-base status gradually stabilises and restored to normal. Note that there must have been a significant K⁺ deficit due to the amount of KCl needed to return plasma levels to normal (note that we would need urinary K⁺ to verify). Lactate is still mildly elevated.

Blood gas data (\(P_{aCO_2}\), \(PaO_2\), pH, \([HCO_3^-]\), BE, \(SaO_2\), [Hb]) provides useful information on three physiological processes which may lead to acid-base disturbances:

1. **Alveolar ventilation** – equation (1)
   a. Hypercapnia, hypocapnia

2. **Oxygenation** – alveolar gas equation (2), oxygen content equation (3)
   a. Hypoxaemia

3. **Acid-base balance** – Henderson-Hasselbalch equation (4)

**Cardiac Arrhythmias**

A 48-year-old man has experienced chest pain radiating into the left arm with exertion or excitement for two years. The pain has become progressively worse, but has never lasted more than 20 minutes at a time. While watching television one evening, he experiences severe chest pain that lasts several hours and is accompanied by sweating and nausea. He is admitted to hospital where his electrocardiogram (ECG) is monitored over 10hrs:

1. **Explain the reversed polarity and increased duration of the QRS complex for the single ectopic beat in A.**

   The QRS complex is derived from the atrioventricular node and is an indication of ventricular depolarisation (i.e. contraction of the ventricles). Under normal circumstances, duration is no longer than 0.10 seconds – longer durations suggest prolonged conduction of the impulse through the ventricles.

   This may be due to cardiac hypertrophy, bundle branch block, pre-excitation of the ventricles via a bypass tract (Wolff-Parkinson-White syndrome) or an ectopic beat. In the case of an ectopic beat, the spread of depolarisation does not follow the normal fast conducting pathways within the heart and the depolarisation wave takes longer to spread through the myocardium.

   Note that the direction of deflection of the trace is indicative of the direction the impulse is travelling with regards to the electrode – as the polarity is reversed, this is suggestive that the abnormal complex is of ventricular origin.

   The T wave often has a potential polarity opposite to that of the QRS complex as the slow conduction of the impulse through the cardiac muscle causes the area first depolarised also to repolarise first. As a result, the direction of current flow in the heart during repolarisation is opposite to that during depolarisation.

2. **Why is conduction generally slowed in ischaemic regions of the heart?**

   Ischaemia depresses the metabolism of cardiac muscle due to lack of oxygen, excess accumulation of carbon dioxide and lack of sufficient nutrients. Often the heart muscle does not die, as blood supply is sufficient to maintain the life of the muscle even though it is not sufficient to allow repolarisation.

   Basically there is a change in the K⁺ concentration gradient – external concentration increases and internal concentration decreases. The total driving force to move K⁺ out decreases, and there is partial depolarisation of the cardiac cell. Na⁺ channels are inactivated and there is a slower raise of membrane potential to threshold (and hence slower rate of
3. **Explain why an ectopic beat may occur in an ischaemic region of the heart**

All cardiac cells demonstrate automaticity in vitro, and can therefore cause ectopic beats or take over normal pacemaker function in vivo. Ectopic foci can lead to either tachycardia or bradycardia depending on their location and surrounding electrical conditions.

Generally, when an ectopic focus drives the rhythm of the heart, spread of depolarisation does not follow the normal conducting pathways and the wave of depolarisation takes longer to spread.

Possible causes of ectopic foci include local areas of ischaemia, small calcified plaques at different point in the heart that press against adjacent cardiac muscle, and toxic irritation of the AV node, Purkinje system or myocardium due to drugs, nicotine or caffeine.

In conditions of ischaemia, the membrane depolarises which closes fast Na⁺ channels. At a membrane potential of around –50mV, all fast Na⁺ channels are closed – action potentials can be elicited, however the inward current is carried by Ca²⁺ (slow) channels.

Intracellular Ca²⁺ rises to the point where it can trigger release of further Ca²⁺ from the junctional sarcoplasmic reticulum and this drives the Na⁺/Ca²⁺ exchanger (which is electrogenic). The resulting action potential is now similar to that found in pacemaker cells in the SA node and displays spontaneous depolarisation and automaticity.

4. **Explain why the ectopic beat occurring during the T wave of the previous ECG in B initiates a series of abnormal QRS complexes (ventricular tachycardia)**

The T wave represents ventricular repolarisation and is generally longer in duration than depolarisation (conduction of the repolarisation wave is slower than the wave of depolarisation).

In an ischaemic part of the heart, there is a substantial mismatch in the repolarisation summation and this produces depression of the ST segment. This indicates that some regions are hyperpolarized while others are depolarised – the direction of the T wave reflects the areas of the heart that is repolarised and whether the wavefront is moving towards or away from the endocardium.

Re-entrant arrhythmia requires a triggering event as well as a block to conduction – both of these factors are much more likely to occur in cases of ischaemia.

5. **Explain what classes of anti-arrhythmic agents would be inappropriate in this case:**

Ca²⁺ channel blockers wouldn’t have an effect on the re-entrant circuit, while drugs affecting the K⁺ or Na⁺ channels certainly would help to alleviate the area of unidirectional block.

**Angina Pectoris**

A 52-year-old man regularly experiences chest pain with moderately vigorous exertion. The pain is heavy in character and is felt across the anterior chest with radiation to the neck and down the left arm. The pain is relieved by a few minutes of rest and is more rapidly resolved by taking a tablet under the tongue, as prescribed by his doctor. When the patient’s treatment is supplemented with the drug propranolol, he no longer has episodes of chest pain with exertion, but experiences early fatigue and muscle pain instead.
1. Explain how the balance of myocardial oxygen supply/demand is altered in exercise

Normal resting \( O_2 \) consumption for a young man is around 250mL/min – however, under maximal conditions this can be increased to between 3600 and 5100mL/min depending on the fitness and training of the individual. There is a linear relation between \( O_2 \) consumption and total pulmonary ventilation at different exercise levels.

However, the respiratory system is not normally the limiting factor in the delivery of \( O_2 \) to the muscles during maximal muscle aerobic metabolism. Rather, it is the ability of the heart to pump blood (delivering \( O_2 \) and nutrients to the muscles).

The actual contractile process temporarily decreases muscle blood flow as the contracting muscle compresses the intramuscular blood vessels (so strong tonic contractions can cause rapid muscle fatigue). Muscular blood flow during exercise can increase markedly (25-fold), mediated by intramuscular vasodilation and other factors (notably the ~30% increase in arterial blood pressure in exercise).

Work output, \( O_2 \) consumption and cardiac output are all directly related to each other – muscle work output increases \( O_2 \) consumption, which in turn dilates muscle blood vessels, increasing venous return and cardiac output. Note that the heart rate increase accounts for a greater proportion of the cardiac output increase, than does the increase in stroke volume during strenuous exercise.

2. What is the pain due to, and why does the patient feel it across the chest with radiation to the neck and down the left arm?

William Heberden first described angina pectoris in 1768 – “There is a disorder of the breast marked with a strong and peculiar symptoms considerable for the degree of danger belonging to it and not extremely rare of which I do not recollect any mention among medical authors. The seat of it and sense of strangling and anxiety with which is attended may make it not improperly be called Angina pectoris. Those who are afflicted with it, are seized, while they are walking, and more particularly when they walk soon after eating with a painful and most disagreeable sensation in the breast.”

Angina may have a number of aetiologies, but the basic physiology is that the load on the heart becomes too great in relation to the coronary blood flow. The characteristic distribution of the pain is due to the embryology – the heart originates near the oropharyngeal membrane, as do the arms. As a consequence both structures receive pain fibres from the same spinal cord segments.

Angina is often precipitated by exercise or when patients experience emotions that increase the metabolism of the heart or cause temporary vasoconstriction (due to sympathetic nervous system activation). The pain usually lasts for a few minutes, but patients with severe ischaemia may have chronic pain.

3. What are the tablets which the patient is taking under his tongue, and how do they relieve his chest pain?

The tablets are probably glyceryl trinitrate – sublingual administration allows absorption through in the buccal mucosa for rapid onset and avoiding 1\(^{st}\) pass metabolism in the liver. Alternatively, glyceryl trinitrate can be administered as a sublingual spray or as prophylactic slow-release patches (removed at night to prevent tolerance developing).

GTN combines with cysteine in vascular smooth muscle \( \rightarrow 5\)-nitrosocysteine \( \rightarrow \) free radical nitric oxide. NO activates cytosolic guanylate cyclase by binding to iron in its haem prosthetic group, and activated guanylate cyclase catalyses cGMP formation.

cGMP-dependent protein kinases mediate smooth muscle relaxation via several possible mechanisms involving protein phosphorylation – activation of Ca\(^{2+}\)-ATPases (increases efflux), inhibition of Ca\(^{2+}\)channels (decreases influx), and hyperpolarization of the sarcolemmal membrane by stimulation of Ca\(^{2+}\)-dependent K\(^+\) channels.

In terms of angina, NO most likely specifically mediates systemic venoconstriction to reduce
the volume stress of the heart. Reducing the constriction of systemic arteries also helps to reduce afterload and preload.

4. **Explain how the drug propranolol prevents the patient from experiencing chest pain with exertion.**

Propranolol is a β-adrenergic receptor blocker and is used to treat angina by reducing afterload, leading to a reduction in myocardial O₂ demand and a decrease in heart rate, improving cardiac perfusion (β₁-mediated effects). Dosage of 80mg-320mg administered orally twice to four times daily have been shown to be effective.

This is achieved by blocking catecholamine-induced increases in heart rate, systolic blood pressure and the velocity and extent of myocardial contraction. In doses greater than those required for β-blockade, propranolol also exerts a quinidine-like membrane action that affects the cardiac action potential (though the significance of this in the treatment of arrhythmia is uncertain).

Propranolol is non-selective and lipid-soluble, and is metabolised by the liver. Note that concurrent administration with Ca²⁺ channel blockers may lead to depressed contractility and AV block as they interfere with hepatic metabolism. It may also reduce myocardial performance in patients with overt heart failure, and is generally contraindicated in patients with asthma or diabetes.

5. **Why is treatment with propranolol associated with early fatigue and muscle pain in exercise?**

The reduction of cardiac output has shifted the problem from cardiac to skeletal muscle and these are the features of tissue hypoxia. Propranolol may also increase myocardial oxygen requirements by increasing left ventricular fibre length, end diastolic pressure, and systolic ejection period.

There have been reports of exacerbation of angina (in some cases, myocardial infarction) following abrupt discontinuation of propanolol therapy – it is recommended that the dosage be gradually reduced over a few weeks if discontinuation of the drug is planned.