F. Acid-Base Physiology

a. Explain and describe acid-base chemistry using the Henderson-Hasselbalch equation.

pH is defined as $-\log_{10}[H^+]$. Normal ECF pH is from 7.35 to 7.45 ([H+] 35-45 nmol/l). Survivable ECF pH is from 6.8 to 7.6. Acids are compounds which donate H$^+$ ions and bases are compounds which accept H$^+$ ions. Organic acid and bases in solution are partially dissociated, according to the pH of their surroundings and their pKa. pKa is defined as the pH at which half of the quantity of an acid is dissociated in solution. The relationship between pH, pKa and the dissociation of an acid or base is described by the Henderson-Hasselbalch equation:

$$\begin{align*}
\text{H}^+ + \text{A}^- & \leftrightarrow \text{AH} \\
pH & = \text{pKa} + \log \frac{[\text{A}^-]}{[\text{AH}]} 
\end{align*}$$

Where AH is an acid and A$^-$ its corresponding base. In ECF, examples of organic acids include many proteins such as haemoglobin, lactic acid and ketone bodies. Examples of simple acids include phosphoric and carbonic acid.

b. Describe the chemistry of buffer mechanisms and explain their relevant roles in the body.

A buffer is an acid/base pair which reversibly dissociates. A buffer acts to stabilize the pH of a solution as the introduction or removal of H$^+$ from a buffered solution is partially compensated for by a change in the relative concentrations of the forms of the buffer according to the Henderson-Hasselbalch equation which results in a return of the pH towards its initial value. This is most readily seen in the transformation of the equation:

$$K_a = \frac{[\text{A}^-][\text{H}^+]}{[\text{AH}]}$$

Any rise in [H$^+$] will result in recombination of H$^+$ and A$^-$ to form AH to maintain the constant $K_a$. (H$^+$ + A$^-$ $\rightarrow$ AH) A fall in H$^+$ or a rise in OH$^-$ will have the opposite effect. Most organic acids are capable of acting as buffers. The maintenance of pH in a very tight range is vital for the normal function of most physiological processes. The activity of most enzymes is highly pH dependent. The principle buffers in the blood are:

- Haemoglobin which allows dissociation of some of its 38 histidine residues (HHb $\leftrightarrow$ H$^+$ + Hb$^-$). This is also responsible in part for the right shift of the Hb-O$_2$ dissociation curve with a fall in pH.
- Plasma proteins (and haemoglobin) bearing carboxyl or amine groups (RCOOH $\leftrightarrow$ RCOO$^-$ + H$^+$ or RNH$_2$ $\leftrightarrow$ RNH$^+$ + H$^+$).
- Carbonic acid which is itself in equilibrium with P$CO_2$ (CO$_2$ + H$_2$O $\leftrightarrow$ H$_2$CO$_3$ $\leftrightarrow$ HCO$_3^-$ + H$^+$). This provides for the compensation for pH changes by changes in respiration.

Interstitial fluid contains little haemoglobin or protein and is buffered by carbonic acid. Intracellular fluid is buffered by proteins as described above and also by phosphate (H$_2$PO$_4^-$ $\leftrightarrow$ HPO$_4^{2-}$ + H$^+$).

c. Describe the regulation of acid-base balance.

The second line of regulation of pH (after buffers), is in the respiratory and renal regulation of acid-base balance. The major buffer in extracellular fluid is the carbon dioxide/carbonic acid/carbonate system, catalyzed by carbonic anhydrase:
The extracellular CO$_2$ concentration is regulated by respiration. If an increase in metabolic activity or a fall in pH occur, P$_{CO_2}$ rises. An increase in ventilation increases the rate of elimination of CO$_2$ from the lungs, bringing P$_{CO_2}$ back to normal and raising pH. The reverse occurs when a rise in pH causes a fall in P$_{CO_2}$.

A doubling in alveolar ventilation can compensate for a fall of 0.2 in pH and a halving for a rise of about 0.25. The capacity for changing alveolar ventilation ranges from almost 0 to 15 times normal. Reducing ventilation to compensate for a rise in pH is limited by the requirement to maintain P$_{O_2}$.

The control of ventilation is directly affected by pH. The effectiveness of the whole mechanism is 50-75% and the time to equilibrium 3-12 minutes. The system is impaired by respiratory disease, with COAD patients developing a respiratory acidosis because of their limited ventilation and a greatly impaired ability to compensate for a metabolic acidosis.

The extracellular concentrations of HCO$_3^-$ and H$^+$ as well as non-volatile acids are regulated by the kidney. 80mEq/day of H$^+$ are lost in association with non-volatile acids. HCO$_3^-$ is freely filtered at the glomerulus (4320mEq/day). In the proximal convoluted tubule and loop of Henle H$^+$ is secreted into the tubule by secondary transport in exchange for Na$^+$. H$^+$ combines with filtered HCO$_3^-$ to form CO$_2$ which diffuses into tubule cells and generates H$^+$ and HCO$_3^-$ which diffuses back into the ECF. The net effect is resorption of HCO$_3^-$.

The ammonia buffer in the urine is generated by the metabolism of glutamine in PCT cells to produce 2HCO$_3^-$ which diffuse into the ECF and 2NH$_4^+$ which are transported into the urine by Na$^+$ exchange secondary transport. A low pH stimulates the metabolism of glutamine in this way. In chronic acidosis this is the major system for renal compensation.

A minor determinant of renal H$^+$ secretion is the effect of aldosterone in increasing active transport of H$^+$ in the DCT and collecting ducts.

Infusion of acid buffering

- immediate HCO$_3^-$ buffering in plasma
- ISF equilibrium in 15 minutes
- ICF equilibrium in 2-4 hours
  - with Hb, HPO$_4^{2-}$, other proteins
  - H$^+$ displaces K$^+$ (and Na$^+$) from ICF → hyperkalaemia
  - Cl$^-$ and HCO$_3^-$ enter cells with H$^+$

physiological effects

- shifts O$_2$ dissociation curve to the right
- sensed by carotid and aortic bodies
- respiratory stimulation → partial compensation limited by initial rise in CSF pH

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**Acid-base**

1.F.2

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Acid-base disorders can be categorized as acidaemia or alkalaemia, acidosis or alkalosis, respiratory or metabolic. This classification can be determined from the pH, PCO₂, and HCO₃⁻ in arterial blood. Their normal values are 7.4, 40mmHg and 24mEq/l respectively. A respiratory acidosis results from underventilation, resulting in increased PCO₂, low pH and compensatory rise in HCO₃⁻. A respiratory alkalosis results from overventilation, with a high pH, low PCO₂ and lowered HCO₃⁻. A metabolic acidosis displays a low pH, primary low HCO₃⁻ and compensatory low PCO₂. A metabolic alkalosis has a high pH, high HCO₃⁻ and raised PCO₂.

These problems do not always occur in isolation. Combined respiratory and metabolic acidosis is common in patients with multiple medical problems. The compensatory mechanisms require time to stabilize the pH: 6 to 12 hours for respiratory compensation and 3 to 5 days for renal compensation.

A graph of [HCO₃⁻] versus pH with PCO₂ isobars is used to readily classify acid-base disturbances. Alternatively rule-of-thumb equations can be used to relate “expected” [HCO₃⁻] and PCO₂.

Management of acid-base disturbances in the acute setting focuses primarily on the underlying cause. Respiratory acidosis can be corrected by increasing ventilation. Respiratory alkalosis can be corrected by reducing ventilation within the limits of maintaining adequate oxygenation. Sometimes, for example in neurosurgical procedures, a respiratory alkalosis is desirable and deliberately generated by hyperventilation.

Metabolic acidosis
- high anion gap
  - ketoacidosis, lactic acidosis, ethylene glycol poisoning, renal failure
- normal anion gap
  - loss of HCO₃⁻
    - GIT fluid loss (diarrhoea, drains, ureteroenterostomy)
    - renal tubular acidosis, interstitial disease
    - recovery from ketoacidosis
- drugs: carbonic anhydrase inhibitors, absorbable acids

Metabolic alkalosis
- renal
  - K⁺ depletion, Cl⁻ depletion and volume depletion all ↑ H⁺ loss
    - seen in diuretic use, prolonged vomiting
    - Conn’s syndrome: ↑ aldosterone, ↑ H⁺ loss
- drugs
  - oral (or IV) HCO₃⁻