B. 7 Gas transport in the blood

a. Describe the carriage of oxygen in blood.

Oxygen is carried either bound to haemoglobin or dissolved in solution. The solubility of oxygen in blood is 0.003 ml/100 ml/mmHg so normal arterial blood contains about 0.3 ml/100 ml. The large proportion of oxygen in the blood is bound to haemoglobin, a protein tetramer with an iron-porphyrin ring attached to each chain. Oxygen coordinates with each Fe atom, inducing a conformational change which promotes the binding of oxygen to the other Fe atoms. The total oxygen binding capacity of haemoglobin in blood (at normal pH, temperature and PCO₂) is 1.39ml/g, giving a total oxygen carrying capacity of blood with an Hb of 150 g/l of 20.8 ml/100 ml. Normal arterial blood has a PO₂ of 100 mmHg and is 97.5% saturated; venous blood has a PO₂ of 40 mmHg and is 75% saturated.

b. Explain the oxyhaemoglobin dissociation curve and factors that may alter it, such as carbon monoxide, temperature, carbon dioxide, hydrogen ion concentration and 2,3 diphosphoglycerate.

Normal adult haemoglobin (Hb A) consists of two α and two β chains composing a tetramer. Each chain surrounds a porphyrin ring and Fe²⁺ ion. An oxygen molecule can coordinate with each Fe²⁺ ion, inducing a conformational change in the tetramer from its tense (T, deoxy) to relaxed (R, oxy) state. This change requires the breakage of salt links within each chain and extrusion of 2,3 DPG (2,3 bisphosphoglycerate) from a site where it binds both β chains. The conformational changes with oxygen binding are cooperative, resulting in the sinusoidal shape of the dissociation curve.

2,3 DPG has a major effect on the affinity of Hb for oxygen. It is present within erythrocytes at approximately the same molar concentration as Hb. It is a highly negatively charged molecule:

\[
\text{PO}_4^{2-} - \text{CH}_2 - \text{CHPO}_4^{2-} - \text{COO}^-
\]

which in the tense state of Hb occupies a site in the centre of the tetramer where it binds three positively charged sites on each β chain. This binding must be broken when Hb binds oxygen. This greatly reduces the affinity of Hb for oxygen. In the complete absence of 2,3...
DPG, Hb is 50% saturated at 1 mmHg PO₂ instead of at 26 mmHg. The concentration of 2,3 DPG varies slightly in the erythrocyte, rising with glycolysis in anaerobic conditions and thus promoting the release of oxygen in the presence of hypoxia.

\[
\begin{align*}
G-6-P & \downarrow \\
3\text{-phosphoglyceraldehyde} & \rightarrow 2,3\text{-DPG mutase} \\
1,3\text{-bisphosphoglycerate} & \rightarrow 2,3\text{-bisphosphoglycerate (2,3-DPG)} \\
3\text{-phosphoglycerate} & \rightarrow 2,3\text{-DPG phosphatase} \\
& \text{pyruvate}
\end{align*}
\]

A rise in PCO₂ or in H⁺ ion concentration also promotes the release of oxygen (moving the dissociation curve to the right). This occurs as both CO₂ and H⁺ compete to bind to Hb, which plays a major role in pH buffering. CO₂ reacts with the α NH₃ groups of Hb, reversibly forming a carbamate which forms salt bridges and helps stabilize the T form. H⁺ similarly binds more readily to aspartate and histidine residues which display a rise in pKa with the conformational change from R to T state. This linkage of the affinity for oxygen and H⁺ and CO₂ binding sites on Hb through conformational change is known as the Bohr Effect.

Temperature rise reduces the affinity of Hb for oxygen, producing a right shift in tissues which are substantially above normal temperature, such as exercising muscles. Carbon monoxide binds to Hb about 240 times as avidly as oxygen, having a P₅₀ of about 0.1 mmHg. It coordinates similarly with the Fe²⁺ ion and moves the oxygen dissociation curve to the left.

Other factors which move the curve to the left include high altitude (due to alkalosis), neonatal haemoglobin and thalassaemia. Factors which move the curve to the right include: Hb S, anaemia, hyperthyroidism and normal physiology in the infant (not neonate). More detail in Monitoring (3.B.2)

c. Describe the carbon dioxide carriage in blood including the Haldane effect and chloride shift.

CO₂ is carried in three ways in blood, as dissolved CO₂, as HCO₃⁻, and combined with proteins as carbamino compounds. It is far more soluble in blood than O₂, with about 0.06ml/100ml/mmHg dissolving. In solution it is in equilibrium with carbonic acid and bicarbonate ion:

\[
\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{HCO}_3^- + \text{H}^+
\]

which reacts only slowly in plasma but rapidly within red cells where carbonic anhydrase catalyzes the first reaction.

HCO₃⁻ formed within red cells diffuses easily back into plasma in exchange for Cl⁻ ion, according to the Gibbs-Donnan equilibrium in which diffusible ions distribute themselves such that their concentration ratios are equal between compartments. This movement of Cl⁻ is known as the chloride shift.

The H⁺ ion formed inside red cells does not diffuse readily into plasma as the cell membrane is relatively impermeable to cations. It partly buffered by binding to deoxygenated Hb, helping to stabilize the T form. This buffering allows a greater amount of CO₂ to be carried as HCO₃⁻ than would otherwise be possible. The net increase in CO₂ carrying capacity of blood when it is deoxygenated is known as the Haldane effect.

Some CO₂ is also carried in combination with globin by reacting with terminal NH₂ groups to form carbamates: Hb-NH-COO⁻. This reaction is also facilitated by the deoxygenation of haemoglobin.

Of the total CO₂ content of arterial blood, 90% is as HCO₃⁻, and 5% each dissolved CO₂ and carbamino compounds. However, of the amount of CO₂ exchanged between tissues and lungs, only 60% is carried as HCO₃⁻, 30% as carbamino compounds and 10% dissolved.
d. Explain the carbon dioxide dissociation curve and its clinical implications.

The carbon dioxide dissociation curve of blood is more evenly sloped and steeper than that of oxygen. The major component of the total CO$_2$ concentration is HCO$_3^-$ ion which over the physiological range varies almost linearly with PCO$_2$. The contribution of carbamino compounds varies very little with PCO$_2$, but strongly with the proportion of oxyhaemoglobin, favouring the uptake of CO$_2$ in the tissues where PO$_2$ is low.

A rise in temperature reduces the solubility of CO$_2$ in blood.

The shape of the dissociation curve makes CO$_2$ transport less dependent on V/Q matching, as the contribution of high V/Q alveoli can compensate for that of low V/Q ones, as neither lies on a “plateau” on the curve.

The substantial contribution from CO$_2$ not bound to Hb makes CO$_2$ transport much less dependent upon Hb concentration than O$_2$ transport is.

e. Describe the oxygen and carbon dioxide stores in the body.

The total body stores of oxygen are small compared with the basal requirements for metabolism:

<table>
<thead>
<tr>
<th>Compartment</th>
<th>On Air</th>
<th>100% O$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs (at FRC)</td>
<td>270 ml</td>
<td>1800 ml</td>
</tr>
<tr>
<td>Blood</td>
<td>820 ml</td>
<td>910 ml</td>
</tr>
<tr>
<td>Interstitial fluid</td>
<td>50 ml</td>
<td>55 ml</td>
</tr>
<tr>
<td>Myoglobin-bound</td>
<td>200 ml</td>
<td>200 ml</td>
</tr>
</tbody>
</table>

thus any change in gas exchange results in a rapid change in arterial and tissue PO$_2$ ($t'/2$ about 30 s). Breathing 100% O$_2$ results in an increase in the lung store, but increases the blood content by only 50 ml bound to Hb and 50 ml dissolved. O$_2$ consumption can be approximated using the Brody formula where BW is weight in kg and VO$_2$ is in ml/min:

$$\dot{V}O_2 = 10.15 \cdot BW^{0.73}$$

The total body stores of carbon dioxide are very large and conform best to a multi-compartment model. The blood and interstitial fluid of well-perfused organs represents a rapid compartment which equilibrates with alveolar CO$_2$ in minutes. Less well perfused organs such as skeletal muscle produce a medium compartment and poorly perfused tissue (fat) and carbonates bound in bone compose the largest and very slow compartment.

The blood content of CO$_2$ is about 2.5 l and total body stores about 120 l. Because of the multiple compartments, arterial PCO$_2$ does not equilibrate as quickly following a fall in ventilation as following a rise. Hyperventilation can deplete blood CO$_2$ rapidly ($t'/2$ about 3 min). Apnoea causes a slower rise in PCO$_2$, because the normal rate of production at rest is small compared with the capacity for excretion and equilibrates into the medium compartment as well as blood and alveolar gas. PCO$_2$ rises 3-6 mmHg/min with a $t'/2$ to equilibrium of about 15 min. In practice this allows for Ben-Jet ventilation with oxygen to provide adequate oxygenation and build up a CO$_2$ surplus over 15 or 20 minutes without harmful effects.