Chloride shift/Hamburger phenomenon:

The greater proportion (70%) of carbon dioxide is transported in the form of bicarbonates.

The CO2 reacted with the water of the cytoplasm in the presence of enzyme carbonic anhydrase to form carbonic acid.

The carbonic acid (H2CO3) is a weak acid, which undergoes partial dissociation to yield hydrogen ion (H+) and bicarbonate ion (HCO3-).

The given reaction mostly occur inside RBCs, because the enzyme carbonic anhydrase is abundant there.

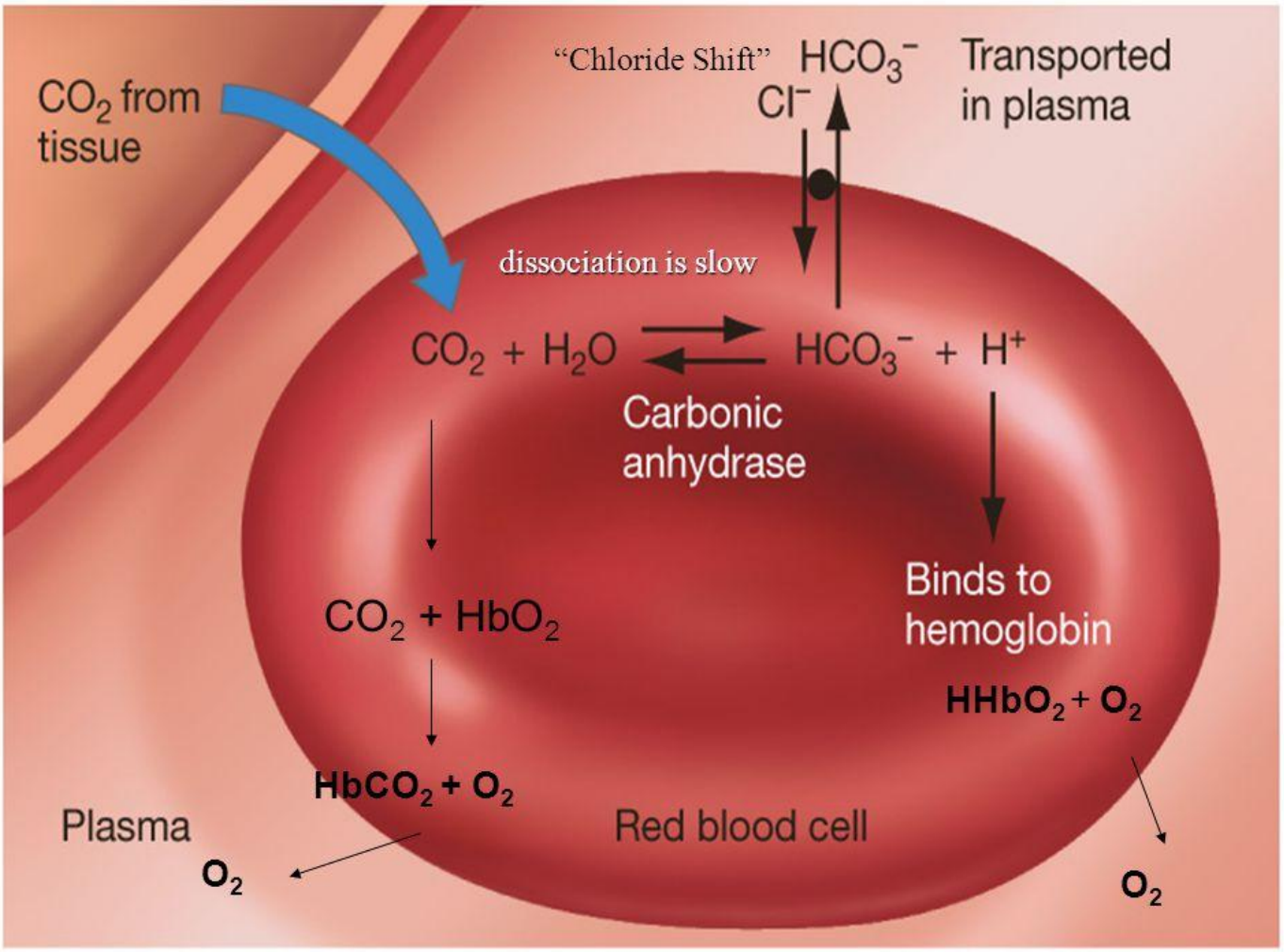


Fig. Diagrammatic representation of chloride shift.

In RBCs, CO2 combines with water to from carbonic acid which dissociates to give H+ ion and bicarbonate (HCO3-) ion in the presence of enzyme carbonic anhydrase.

The bicarbonate ion then diffuses outside the RBC in the plasma and combines with Sodium ions to from Sodium bicarbonate (NaHCO3).

Loss of bicarbonate ions from RBC causes positive charge inside RBC which is balanced by diffusion of chloride (Cl-) ion from plasma into the RBC.

This exchange of Cl- ion and HCO3- ion between plasma and RBC is known as chloride shift.

This phenomenon of chloride shift maintain the electrical neutrality of cell.

This phenomenon is also known as Hamburger phenomenon.

Reverse of chloride shift occurs in tissues.

Definition of the chloride shift:

Westen & Prange (2003) define the chloride shift as:

"the movement of chloride ions from the plasma into red blood cells as blood undergoes the transition from arterial to venous gas partial pressures"

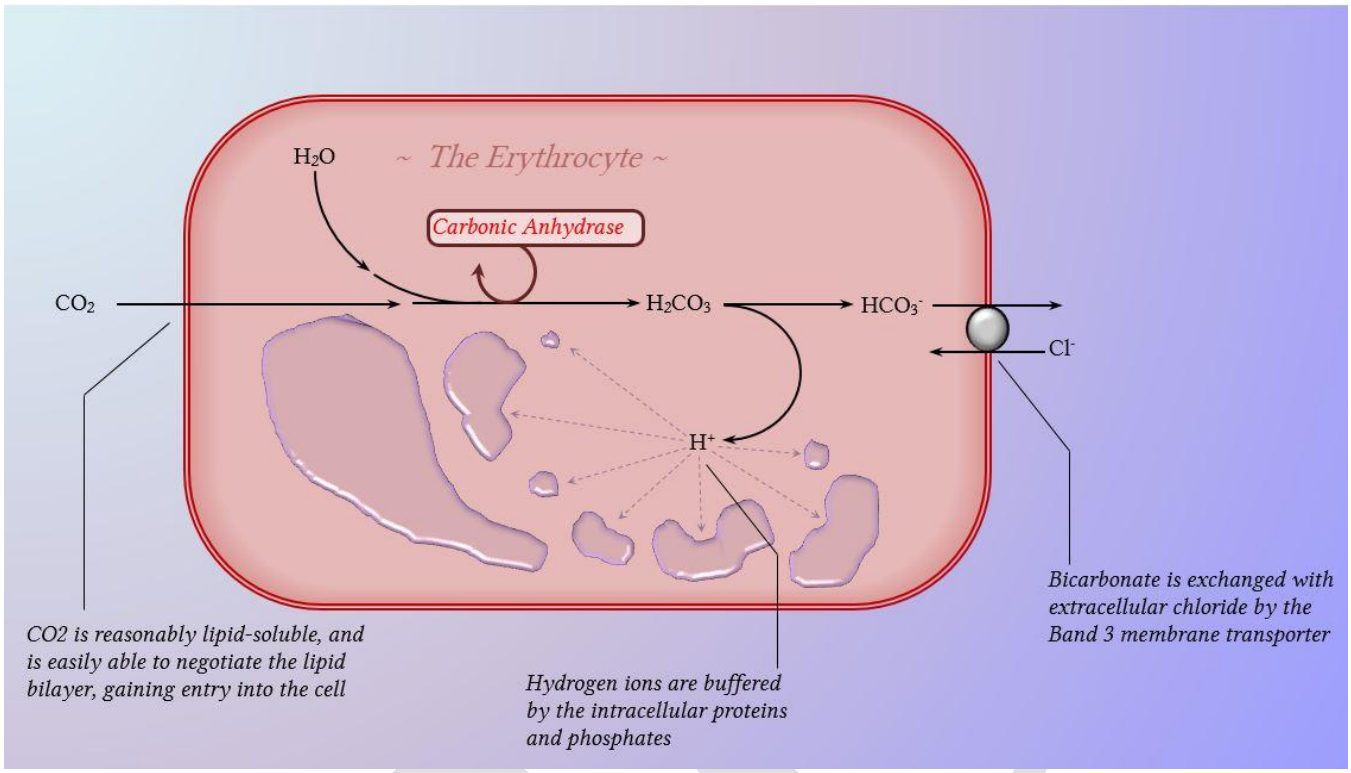
The most important points are:

Chloride moves into erythrocytes, and bicarbonate moves out, in venous blood.

The reverse events take place in the pulmonary capillaries.

Mechanism of the chloride shift

The molecular mechanisms for the chloride shift are described in detail below. In summary, this phenomenon is only possible because of the presence of carbonic anhydrase in RBCs. It is seen as a critically important element (as it is concentrated there, but essentially absent from the bloodstream otherwise). Without it, the reaction converting CO2 to HCO3- would be slow. With massive amounts of erythrocyte carbonic anhydrase, we can instead count on these molecular transactions to be complete in the space of one circulatory time. In fact, because all the required proteins are available in massive concentrations, the reaction is incredibly fast. Wieth & Brahm (1980) had determined that 99% of the chloride shift process is complete within about 700 milliseconds.



In summary:

In the peripheral capillary and venous blood:

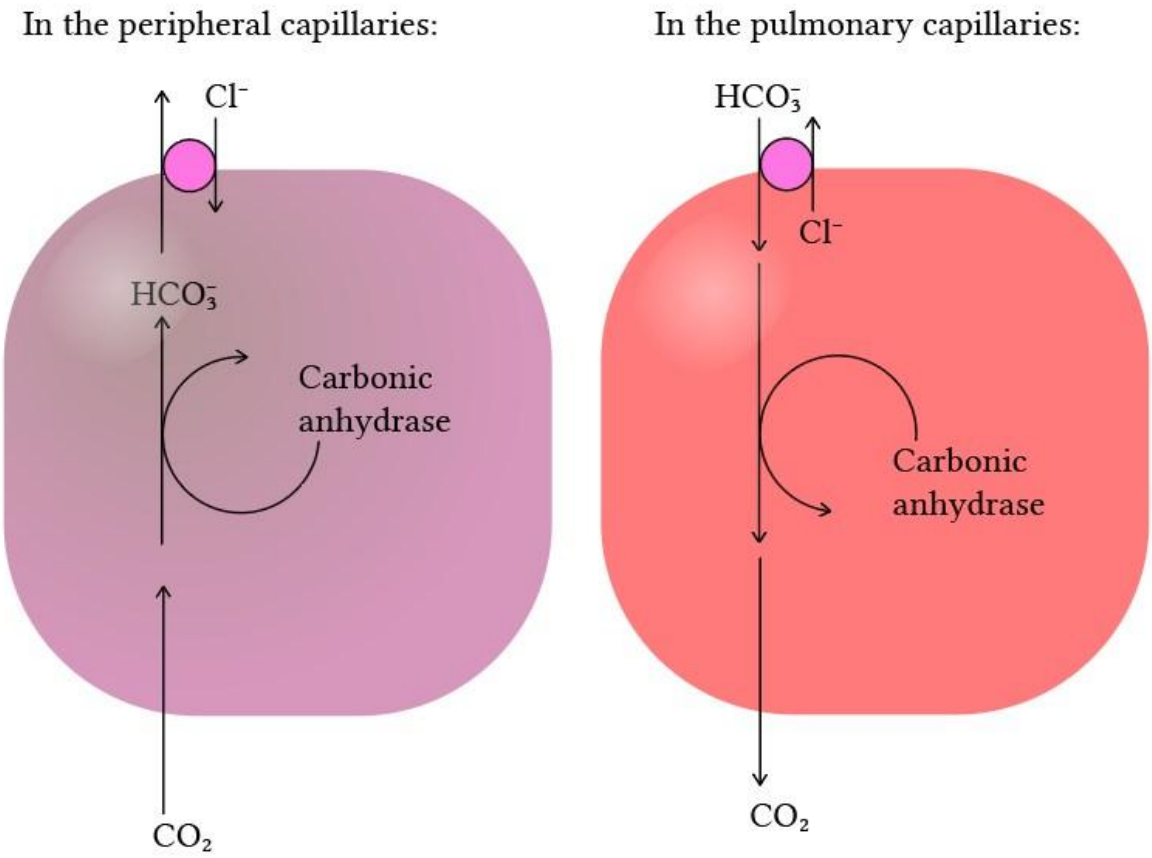
1. CO2 diffuses into the red cells.
2. When the partial pressure CO2 increases in the peripheral capillary blood due to cellular respiration, it enters the red cells fairly easily (as it is lipid-soluble).
3. Klocke (1988) mentions offhand that its diffusion is slowed perhaps 60% by the increased viscosity of the red cell cytosol, but this is not a massive problem because the diffusion distance is about one micrometre.

4. CO_2 is converted into bicarbonate.
5. Here, in the cytosol, the deoxygenated haemoglobin has been acting as a proton-accepting buffer, which has increased the pH of the cytosol.
6. The increased pH facilitates the conversion of CO_2 into bicarbonate by carbonic anhydrase.
7. The protons produced by this process are buffered by intracellular phosphates and proteins (again, mainly deoxygenated haemoglobin).
8. The bicarbonate is exchanged for chloride by the Band 3 exchange protein, i.e. bicarbonate is removed and chloride is shuttled into the erythrocyte to maintain a neutral electrical charge.
9. "Band 3" is the super-imaginative name given to the bicarbonate-chloride exchanger by Fairbanks et al (1971), for whom it was the third protein band from the top in the gel electrophoresis of red cell membranes.
10. It would have been quite a fat band, as Band 3 accounts for about 25% of the total RBC membrane protein content, with over one million transport sites per cell.

11. If it were not for the presence of haemoglobin, RBCs could easily be mistaken for a cell type responsible mainly for carrying chloride.

In the pulmonary capillaries and arterial blood:

- Oxygen binds to haemoglobin and causes it to release protons, i.e. decreases its buffering capacity.
- The fall in RBC cytosolic pH results in the reverse conversion of bicarbonate into CO2 and water.
- CO2 is then removed from the reaction by alveolar ventilation.
- As the concentration of bicarbonate in the cell falls, more bicarbonate is exchanged with chloride by the Band 3 protein.
- Thus, there is a net decrease of bicarbonate in the blood, and a net increase in chloride.
- This whole thing is represented in the pictures below:



Venous blood	
Na^+	135
K^+	5.0
Cl^-	102
HCO_3^-	25.2

Arterial blood	
Na^+	135
K^+	5.0
Cl^-	104
HCO_3^-	23.0

The above numbers came from Western & Prange (2003), whose experiments are discussed below.

Magnitude of the chloride shift:

After determining what electrolyte movements should occur using quantitative

physicochemical analysis, Western & Prange (2003) drained blood from healthy volunteers and subjected it to "venous-ification" by exposure to a hypoxic and hypercapnic atmosphere. At a simulated venous gas concentration, the average chloride shift of the samples was approximately 2.4 mmol/L. With a higher haematocrit, closer to 0.55 (they cheated by centrifuge but there really are people out there with such haematocrit values) the investigators were able to measure a chloride shift of around 4.3 mmol/L.

Significance of the chloride shift:

1.Mitigation of pH change in the peripheral circulation: pH of the peripheral blood would change significantly more if deoxygenated RBCs were not there to buffer the acid and sequester the chloride.

2.Increase in the CO2 carrying capacity of the blood: the effect of shuttling chloride into the red cells and bicarbonate out of them increases the total potential bicarbonate carriage by the venous blood, which is good because most CO2 is carried as bicarbonate.

3.Liberation of O2: just as CO2, chloride is an allosteric modulator of the haemoglobin molecule. Chloride binding to the haemoglobin molecule stabilises it in the T-state,

making oxygen available to the tissues. In humans, this role is probably not dominant, but in other animals it may actually be the main mediator of oxygen loading and unloading. Brix et al (1990) found that the brown bear (Ursus arctos) the chloride shift was massive (a total difference of 33 mmol/L), accounting for 40% of the total oxygen unloading in the peripheral circulation, i.e. it is the dominant modulator of the oxygen-haemoglobin association relationship.