Update in
Anaesthesia

Originally published in Update in Anaesthesia, edition 21 (2006) and reprinted from 'Continuing Education in Anaesthesia, Critical Care and Pain' by kind permission of the Board of Management and Trustees of the British Journal of Anaesthesia

Carbon Dioxide Transport

GJ Arthurs*, M Sudhakar
*Correspondence Email: gja@arthurs40.freeserve.co.uk

Summary

Carbon dioxide is transported in the blood in three ways:

(i) dissolved in solution;

(ii) buffered with water as carbonic acid;

(iii) bound to proteins, particularly haemoglobin.

At a haemoglobin concentration of 15g.dl^{-1}, and a mixed venous PCO_2 of 6.1kPa, venous blood contains 52ml.dl^{-1} carbon dioxide; arterial blood with a PCO_2 of 5.3kPa contains 48ml.dl^{-1}. The effects of carbon dioxide production in the tissues include: increased plasma Cl^-; increased red blood cell mean corpuscular volume; and haemoglobin becoming less acidotic than oxygenated haemoglobin.

INTRODUCTION

Carbon dioxide is produced by cell metabolism in the mitochondria. The amount produced depends on the rate of metabolism and the relative amounts of carbohydrate, fat and protein metabolized. The amount is about 200ml.min^{-1} when at rest and eating a mixed diet; this utilizes 80% of the oxygen consumed, giving a respiratory quotient of 0.8 (respiratory quotient = rate of carbon dioxide production divided by rate of oxygen consumption). A carbohydrate diet gives a quotient of 1 and a fat diet 0.7.

CARBON DIOXIDE TRANSPORT IN THE BLOOD

Carbon dioxide is transported in the blood, from the tissues to the lungs in three ways: (i) dissolved in solution; (ii) buffered with water as carbonic acid; (iii) bound to proteins, particularly haemoglobin.

Approximately 75% of carbon dioxide is transported in the red blood cell and 25% in the plasma. The relatively small amount in plasma is attributable to a lack of carbonic anhydrase in plasma, so association with water is slow; plasma plays little role in buffering and combination with plasma proteins is poor.

There is a difference between the percentage of the total carbon dioxide carried in each form and the percentage exhaled from them. For example, 5% of the total is in solution but 10% of exhaled carbon dioxide comes from this source; 10% is protein bound, particularly with haemoglobin, but this supplies 30% of the exhaled amount.

Dissolved carbon dioxide

Carbon dioxide is 20 times more soluble than oxygen; it obeys Henry's law, which states that the number of molecules in solution is proportional to the partial pressure of the gas at the liquid surface. The carbon dioxide solubility coefficient is 0.0308mmol.l^{-1}.mmHg^{-1} or 0.231mmol.l^{-1}.kPa^{-1} at 37°C. Solubility increases as the temperature falls.

This corresponds to 0.5ml.kPa^{-1} carbon dioxide in 100 ml blood at 37°C. The partial pressure of carbon dioxide is 5.3pKa in arterial blood and 6.1kPa in mixed venous blood; therefore, arterial blood will contain about 2.5ml per 100ml of dissolved carbon dioxide and venous blood 3ml per 100ml. A cardiac output of 5l.min^{-1} will carry 150ml of dissolved carbon dioxide to the lung, of which 25ml will be exhaled. Because of this high solubility and diffusion capacity, the partial pressure of carbon dioxide in alveolar and pulmonary end-capillary blood are virtually the same. Even a large shunt of 50% will only cause a end-pulmonary capillary/arterial carbon dioxide gradient of about 0.4kPa.

Carbonic acid

Carbon dioxide combines with water to form carbonic acid, a reaction accelerated by carbonic anhydrase. The carbonic acid then freely dissociates (Equation 1):

$$CO_2 + H_2O \underset{\text{carbon anhydrase}}{\rightleftharpoons} H_2CO_3$$

$$H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

The enzyme carbonic anhydrase is present in a number of organs of the body including the eye, kidney and brain; however, for this purpose, it is the red blood cell carbonic anhydrase that is important. Once carbonic acid is formed it dissociates easily so that the ratio of $H_2CO_3^-$ to HCO_3^- is 1:20 (Equation 2).

$$\frac{CO_2}{H_2CO_2} = \frac{1000}{1} \qquad \frac{H_2CO_2}{HCO_3^-} = \frac{1}{20}$$

Carbon dioxide and water diffuse freely into the red blood cell and are converted to carbonic acid, which dissociates into hydrogen and bicarbonate ions. Hydrogen ions do not pass through cell membranes but carbon dioxide passes readily. This situation cannot be sustained as the intracellular hydrogen ion and bicarbonate ion concentration, osmolarity and cell size will rise and rupture the cell. The bicarbonate ion diffuses out to the plasma to be exchanged for chloride ions. This is known as the **chloride shift** (Gibbs–Donnan equilibrium or Hamburger effect). An ion exchange transporter protein in the cell membrane called Band 3 for Cl^- and HCO_3^- facilitates chloride shift. A build up of hydrogen ion in the red blood cell would also prevent further conversion and production of bicarbonate ion.

GJ Arthurs
Consultant Anaesthetist
Maelor Hospital
Wrexham LL13 7TD
UK

M Sudhakar
Prince Charles Hospital
Merthyr Tydfil CF47 9DT
UK

However, hydrogen ions bind easily to reduced haemoglobin, which is made available when oxygen is released; therefore, free hydrogen ions are removed from solution. Reduced haemoglobin is less acidic than oxygenated haemoglobin. This is another way of stating the **Haldane effect**, which explains that, at any given pCO_2, the carbon dioxide content of deoxygenated blood is greater than that of oxygenated blood.

As a result of the shift of chloride ions into the red cell and the buffering of hydrogen ions onto reduced haemoglobin, the intercellular osmolarity increases slightly and water enters causing the cell to swell. This can be measured as an increase in mean corpuscular volume (MCV). The reverse process occurs as the red blood cell passes through the lung.

Bound to haemoglobin and other proteins

Carbon dioxide combines rapidly to the terminal uncharged amino groups ($R\text{-}NH_2$) to form carbamino compounds (Equation 3).

$$R\text{-}NH_2 + CO_2 \rightleftharpoons RNH\text{-}CO_2 + H^+$$

In most proteins, it is only the terminal amino acid group that combines with carbon dioxide. Haemoglobin is different when forming carbaminohaemoglobin. Reduced haemoglobin is the only effective protein buffer of hydrogen ion at physiological pH because of its high content of the amino acid histidine. Hydrogen ions attach to the imidazole group of the histidine. About 30% of exhaled carbon dioxide was transported combined with haemoglobin protein.

The amount of carbon dioxide held in blood in the carbamino form is small but it accounts a third of the difference between venous and arterial carbon dioxide content. The Haldane effect reflects the difference in carbon dioxide content between oxygenated and reduced haemoglobin at the same pCO_2. This effect is partly attributable to the ability of haemoglobin to buffer hydrogen ions and partly due to the fact that reduced haemoglobin is 3.5 times more effective in combining with carbon dioxide than oxyhaemoglobin.

Different haemoglobins vary in their affinity for carbon dioxide, carbon monoxide and oxygen. Carbon dioxide combines readily with haemoglobin to form a carbamino bond at a lower partial pressure than oxygen, but haemoglobin carries less than a quarter of the amount of carbon dioxide compared with oxygen. By contrast, foetal haemoglobin combines with oxygen at a lower partial pressure due to the replacement of the b-chain with g-chains. Carbon monoxide has a greater affinity for haemoglobin and so displaces oxygen.

CARBON DIOXIDE TRANSPORT IN THE TISSUES

Carbon dioxide transport in the tissue is summarized in Figure 1. Carbon dioxide combines with water to form carbonic acid. This reaction is very slow in plasma but fast within the red blood cell owing to the presence of the enzyme carbonic anhydrase. Carbonic acid (H_2CO_3) dissociates into H^+ and HCO_3^- ions; therefore, the concentration of both H^+ and HCO_3^- is increased in the red blood cell. HCO_3^- can diffuse out of the red blood cell into plasma whereas H^+ cannot. In order to maintain electrical neutrality, chloride ions diffuse into the red blood cell from the plasma as HCO_3^- diffuses out. Hydrogen ions are taken up by reduced haemoglobin. The imidazole group of the amino acid histidine gives haemoglobin a very significant buffering capacity, not present in other amino acids. This buffering capacity is made possible by the fact that each tetramer of haemoglobin contains 38 histidine residues and the dissociation constant of the imidazole groups of the four histidine residues, to which the haem groups are attached, is affected by the state of oxygenation of the haem. In the acidic state, the oxygen bond is weakened, while reduction of haemoglobin causes the imidazole group to become more basic. In the tissues, the acidic form of the imidazole group weakens the strength of the oxygen bond at the same time as hydrogen ions are being buffered by the more basic haemoglobin.

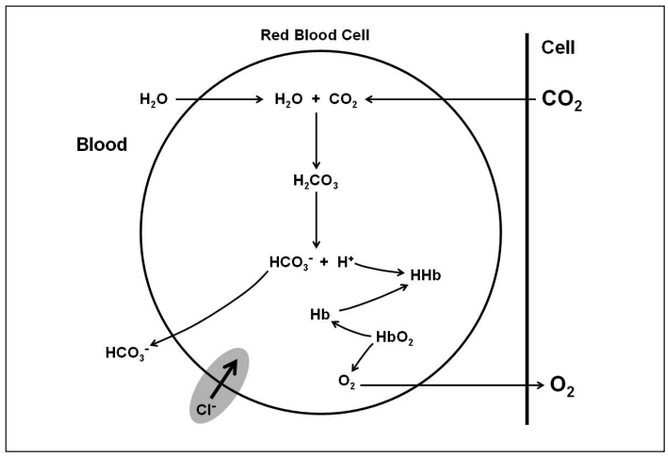

Figure 1. *Movement of gases at tissue level with the chloride shift highlighted*

CARBON DIOXIDE TRANSPORT IN THE LUNGS

The combination of oxygen with haemoglobin is facilitated by the histidine group becoming more basic, which increases the affinity of the haem group for oxygen as the carbon dioxide is lost (Equation 4). This is one reason for the **Bohr effect**.

$$O_2 + HbH^+ + HCO_3^- \rightleftharpoons HbO_2 + H_2O + CO_2$$

Release of Hb shifts the equilibrium in favour of carbon dioxide formation and elimination. HCO_3^- concentration decreases as carbon dioxide is formed and eliminated (Figure 2).

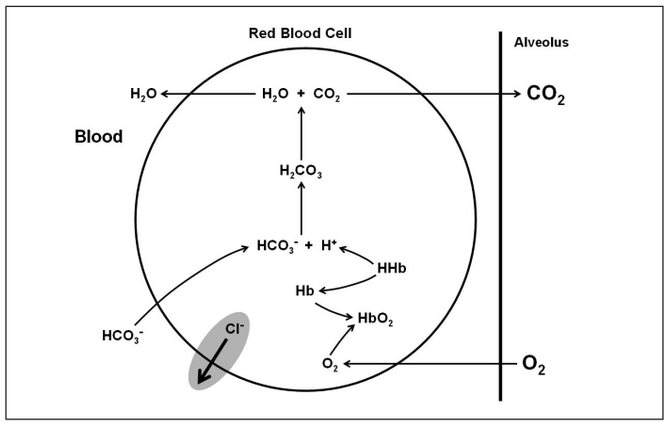

Figure 2. *Movement of gases at alveolar level*

CARBON DIOXIDE DISSOCIATION CURVES

Carbon dioxide dissociation curves relate $PaCO_2$ (kPa or mmHg) to the amount of carbon dioxide (ml) carried in blood (Figure 3). The amount of dissolved carbon dioxide and bicarbonate vary with pCO_2, but are little affected by the state of haemoglobin. However, the amount of carbaminohaemoglobin is much affected by the state of oxygenation of haemoglobin, less so by the pCO_2.

In mixed venous blood, $PvCO_2$ is 6.1kPa (46mmHg) and in arterial blood PaO_2 is 5.3kPa (40mmHg). Total carbon dioxide in venous blood is 52ml per 100ml and in arterial blood 48ml per 100ml. Consequently, the curve is more linear than the O_2Hb dissociation curve.

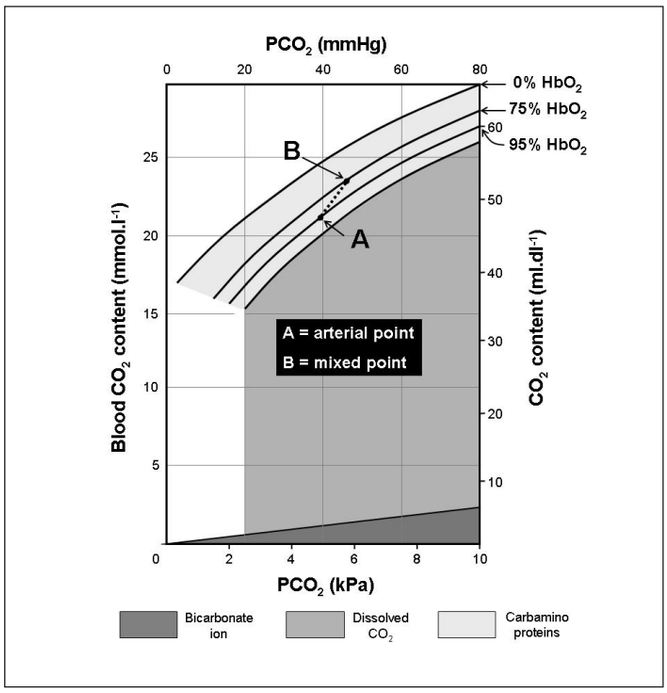

Figure 3. *Total carbon dioxide transport in whole blood*

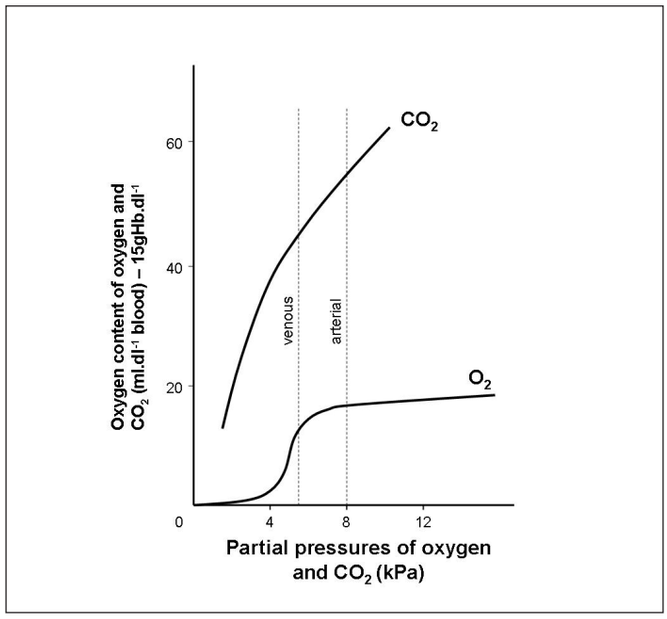

Figure 4. *Partial pressure of oxygen and carbon dioxide*

Figure 4 illustrates the difference between the content in blood of oxygen and carbon dioxide with change in partial pressure. It emphasizes that the carbon dioxide content rises throughout the increase in partial pressure. Oxygen content rises more steeply until a point at which the haemoglobin is fully saturated. After that, the increase is small because of the small increased amount in solution.

DIFFERENCES BETWEEN VENOUS AND ARTERIAL BLOOD

The differences between arterial and venous blood are summarized in Figure 5. The high content of carbon dioxide in venous capillary blood reduces the affinity of haemoglobin for oxygen leading to release of oxygen to the tissues.[1] The oxygen dissociation curve shifts to the right (**Bohr effect**). Deoxygenated haemoglobin takes up more carbon dioxide than oxygenated haemoglobin (**Haldane effect**). Removal of oxygen from haemoglobin in the tissue capillaries causes the haemoglobin molecule to behave more like a base (better proton acceptor). Therefore, haemoglobin increases the amount of carbon dioxide that is carried in venous blood (Equation 4).

$$HbO_2 + CO_2 + H_2O \rightleftharpoons HbH^+ + HCO_3^- + O_2$$

Each carbon dioxide molecule added to the red blood cell increases the intracellular osmotic pressure by an increase in either HCO_3^- or Cl^- ions. Therefore, the red blood cell increases in size and the haematocrit of venous blood is some 3% more than arterial blood. The plasma concentration of chloride ions is lower but bicarbonate ion concentration is greater.

pH OF RED BLOOD CELLS

The total reduction of all haemoglobin would result in a rise in blood pH by 0.03. At 25% oxygen saturation, the pH increases by 0.007 (at constant pCO_2). If the pCO_2 rises by 0.8kPa (6mmHg), i.e. the difference between mixed venous and arterial blood, the pH will reduce by 0.04. The net effect is a fall in pH of 0.033 from 7.4 to 7.36.

CHANGES IN RED BLOOD CELLS DURING PASSAGE THROUGH THE LUNGS

In pulmonary capillary blood, the red blood cell releases carbon dioxide and the haemoglobin affinity for oxygen is increased.

The oxygenated haemoglobin binds fewer hydrogen ions making it more acidic but the fall in pCO_2, and the shift in chloride and bicarbonate ions, makes the red blood cell less acidic. The outward shift of water gives a smaller MCV and reduced haematocrit. The oxygen dissociation curve will shift to the left (Bohr effect). The plasma concentration of chloride ion is higher in arterial compared with venous blood; bicarbonate concentration is lower.

THE ROLE OF CARBON DIOXIDE IN ACID ELIMINATION

Every minute, 200ml of carbon dioxide is exhaled; this is the equivalent to 12–13mol of hydrogen ions in 24h.[2] Urine pH varies from 4.5 to 8.0. A pH of 4.0 represents 10^{-4}mol.l^{-1} of hydrogen ions. Therefore, the passage of 3 litres of urine accounts for a relatively small amount of hydrogen ion elimination in 24 hours; however, this

includes the phosphate and sulphate ions that cannot be converted to carbon dioxide.

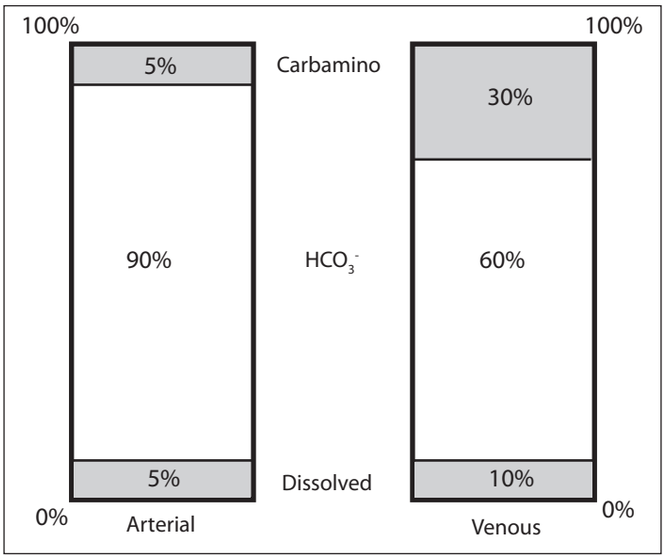

Figure 5. *Distribution of carbon dioxide in arterial and venous blood*

EFFECT OF APNOEA

The total body content of carbon dioxide including bicarbonate ion is 120 litres or 100 times that of oxygen. If there is apnoea and all the carbon dioxide is retained in the body, pCO_2 will rise by 0.4 to 0.8kPa.min^{-1} (3–6mmHg.min^{-1}). Alveolar gas will rapidly equate with venous blood, giving an alveolar pCO_2 rise from 5.3 to 6.1kPa and a pO_2 fall from 14 to 5.3kPa in 1 minute. Therefore, the patient becomes rapidly hypoxaemic. If the patient is pre-oxygenated with oxygen 100%, the arterial oxygen tension will remain above 13kPa and 100% saturation is maintained for several minutes as 250ml.min^{-1} of oxygen is used from a high partial pressure in the lung. However, $PaCO_2$ will steadily rise; after 5min, it will be approaching 10kPa with an associated fall in pH.

REFERENCES

1. West JB. Respiratory Physiology, 7th Edn. Lippincott Williams & Wilkins, 2004.
2. Ganong WF. Review of Medical Physiology, 21st Edn. Lange Medical Books, 2003.
3. Nunn JF. Respiratory Physiology, 5th Edn. Butterworth Heinemann, 1999.