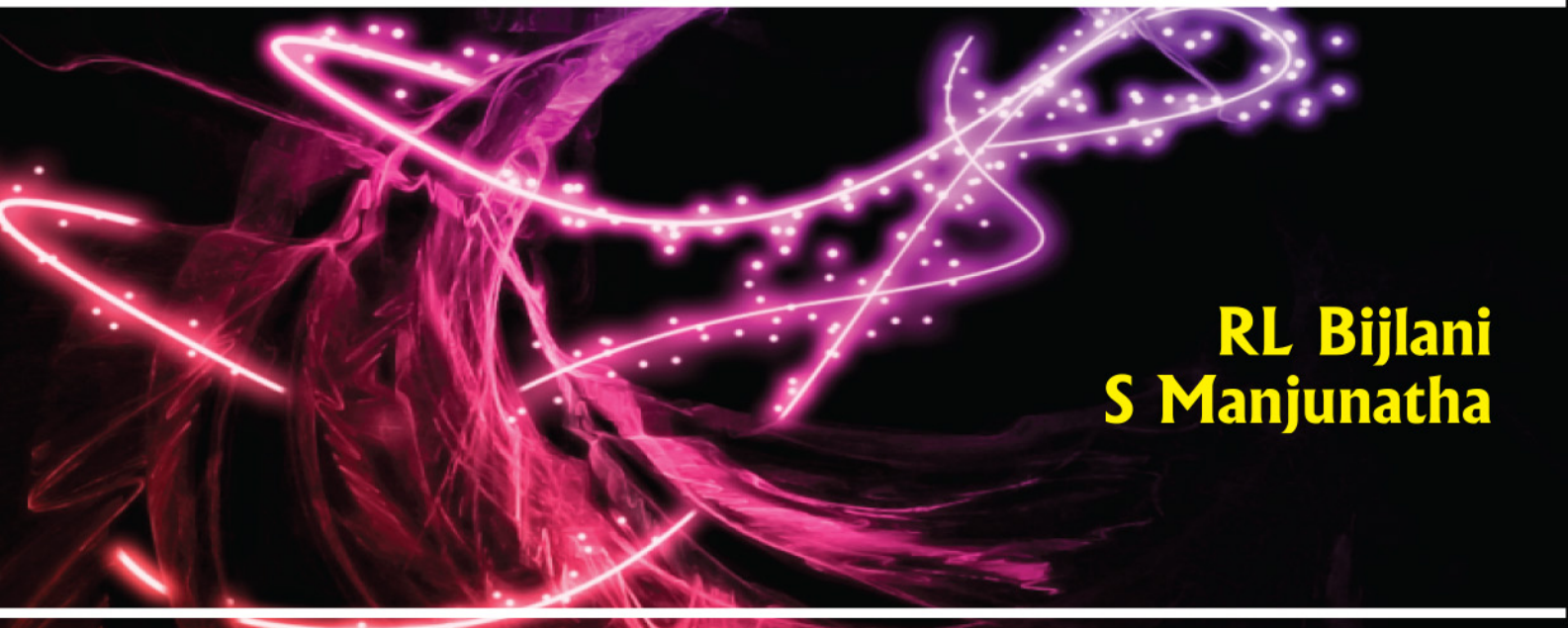
FOURTH EDITION



UNDERSTANDING MEDICAL PHYSIOLOGY

A TEXTBOOK FOR MEDICAL STUDENTS



RL Bijlani
S Manjunatha

JAYPEE

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Chapter

4.3

Carbon Dioxide Transfer, Transport and Expulsion

Metabolic activity utilises oxygen and produces carbon dioxide. Carbon dioxide is a waste product which has to be eliminated from the body to preserve constancy of the internal environment. Elimination of carbon dioxide takes place through a process which is broadly reverse of that by which oxygen is supplied to the tissues (Fig. 4.2.1). Carbon dioxide is picked up from the tissues by the tissue capillaries, transported in the venous blood, and finally expelled in the lungs. We shall consider the three processes of carbon dioxide transfer, transport and expulsion one by one.

CARBON DIOXIDE TRANSFER

Carbon dioxide is transferred from the tissues to capillaries using the interstitial fluid as an intermediary medium. The flow is the result of diffusion, which in turn is due to the higher PCO_2 in cells (about 46 mm Hg) and interstitial fluid (about 45 mm Hg) than in arterial blood (40 mm Hg). As a result of the transfer, the PCO_2 of the blood leaving the tissues (venous blood) rises to 45 mm Hg. The pressure gradient of 5 mm Hg for carbon dioxide transfer is much less than the corresponding gradient for oxygen, although the volume of exchange is nearly the same for both gases. Why do you think a smaller pressure gradient is sufficient for carbon dioxide exchange?[1]

CARBON DIOXIDE TRANSPORT

Carbon dioxide transferred from the tissues to the blood is transported in three forms: as dissolved gas, as bicarbonate, and as carbamino compounds.

Dissolved Carbon Dioxide

Although carbon dioxide is fairly soluble in water, the dissolved form accounts for only about 7% of the carbon dioxide transported. Let us examine why it is so. At body temperature (37°C), the solubility of carbon dioxide is 0.06 mL/mm Hg/100 mL. The arterial PCO_2 is 40 mm Hg. Therefore the volume of carbon dioxide in the dissolved form in arterial blood is $0.06 \times 40 = 2.4$ mL/100 mL. The venous blood, with PCO_2 of 45 mm Hg, carries $0.06 \times 45 = 2.7$ mL/100 mL dissolved carbon dioxide. Thus each 100 mL of venous blood carries only 0.3 mL additional carbon dioxide in the dissolved form as compared to arterial blood. On the other hand, the total carbon dioxide content of arterial and venous blood is 48 mL/100 mL and 52 mL/100 mL respectively. Thus each 100 mL of venous blood transports 4 mL additional carbon dioxide as compared to the arterial blood. Out of these 4 mL, only 0.3 mL is transported in the dissolved form, which amounts to $0.3/4 \times 100 = 7.5\%$. Thus the reason for dissolved carbon dioxide accounting for only a small fraction of carbon dioxide transport is as follows. The amount of dissolved carbon dioxide depends on PCO_2. The difference between the arterial and venous PCO_2 is only 5 mm Hg. Therefore only 0.3 mL additional carbon dioxide is dissolved in each 100 mL of venous blood as compared to the arterial blood. Thus the small difference in PCO_2 between the arterial and venous blood accounts for dissolved carbon dioxide being a poor mechanism for carbon dioxide transport in spite of carbon dioxide being fairly soluble in water.

Carbon Dioxide Transport as Bicarbonate

This is the major mechanism of carbon dioxide transport. Red blood cells (RBCs) play a major role in the mechanism because of the presence of carbonic anhydrase in them as explained below (Fig. 4.3.1).

Carbon dioxide diffuses from the tissues into the interstitial fluid, from the interstitial fluid into the plasma, and from the plasma into the RBC fluids, driven by the PCO_2 gradient. Carbon dioxide dissolves in RBC fluids to form carbonic acid, a process facilitated enormously by the enzyme carbonic anhydrase present in RBC. Carbonic acid dissociates into hydrogen ions and bicarbonate ions. Bicarbonate ions diffuse out of the RBC due to concentration gradient. Hydrogen ions are buffered partly by haemoglobin, and partly by plasma proteins, but still the pH of venous blood falls slightly. Exit of bicarbonate ions from RBC is not accompanied by a comparable exit of cations because the RBC membrane is relatively impermeable to cations. Hence an electrical gradient is created across the RBC membrane, which results in passive transport of some chloride ions from the plasma into RBC (**chloride shift**). The degree of chloride shift is governed by Gibbs-Donnan equilibrium. The efflux of bicarbonate and the influx of chloride is

[1] It is sufficient because carbon dioxide is much more soluble than oxygen. Hence carbon dioxide diffuses about 20 times faster than oxygen. Or, for the same rate of diffusion, only one-twentieth of the pressure gradient is sufficient for carbon dioxide.

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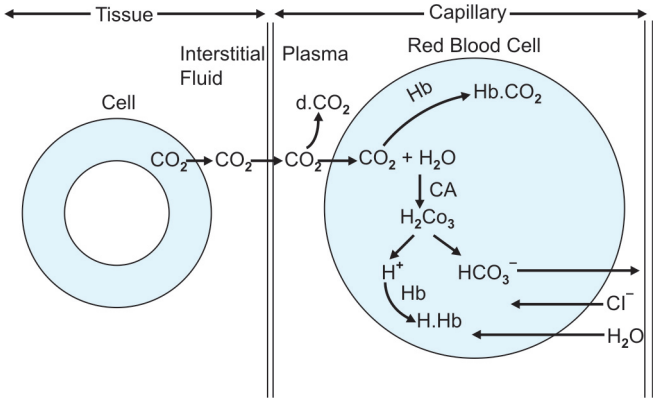

Fig. 4.3.1: Carbon dioxide is transported in the blood as dissolved carbon dioxide (d. CO_2), carbaminohaemoglobin (Hb. CO_2) and as bicarbonate (HCO_3^-). Bicarbonate accounts for 70% of the carbon dioxide transported, and is associated with a few reactions in the red blood cells as shown in the diagram. CA, carbonic anhydrase. Details in text.

facilitated by a bicarbonate/chloride carrier protein in the RBC membrane. Generation of bicarbonate ions and entry of chloride ions raises the osmotic pressure of RBC fluids. As a result, water moves passively from plasma into the RBC. That is why the biconcave RBC of the venous blood are a little rounded (i.e. less concave) than those of the arterial blood.

All the reactions described above proceed in the opposite direction when carbon dioxide is expelled in the lungs. Conversion of carbonic acid into carbon dioxide and water is also catalysed by carbonic anhydrase. That is why carbon dioxide collection from the tissues as well as discharge in the lungs are both impaired by carbonic anhydrase inhibitors, leading to high PCO_2 in tissues as well as blood.

Thus the carbon dioxide picked up from tissues is transported as plasma bicarbonate with the help of RBC carbonic anhydrase. Transport in the form of bicarbonate accounts for about 70% of carbon dioxide transport.

Carbon Dioxide Transport as Carbamino Compounds

Carbon dioxide combines chemically with haemoglobin and several plasma proteins to form carbamino compounds. Since haemoglobin is the most abundant protein in blood, carbaminohaemoglobin is the major compound of this class in blood. Transport in this form accounts for only 20% of carbon dioxide transport.

Carbon Dioxide Dissociation Curve

The overall relationship between PCO_2 and the volume of carbon dioxide carried by blood in all the three forms put together is expressed as the carbon dioxide dissociation curve (Fig. 4.3.2). The position of the curve is affected significantly by PO_2. The effect of PO_2 on the carbon dioxide dissociation curve is called the **Haldane effect.** In order to examine the physiological significance of Haldane effect, let us see the effect of PO_2 on carbon dioxide carriage in the physiological range of PCO_2 (Fig. 4.3.3). As seen in the Figure, at a PO_2 of 100 mm Hg, change in PCO_2 from 40 to 45 mm Hg would result in uptake of only 2 mL CO_2/100 mL blood. But since PO_2 falls to 40

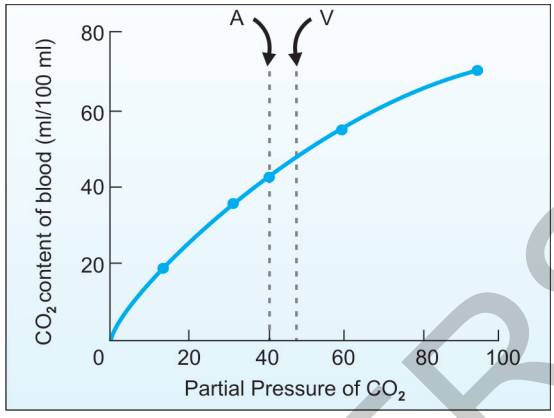

Fig. 4.3.2: Carbon dioxide dissociation curve. The dotted lines indicate the physiological operating range of the curve. A. arterial PCO_2 (40 mmHg); V, venous PCO_2 (46 mmHg).

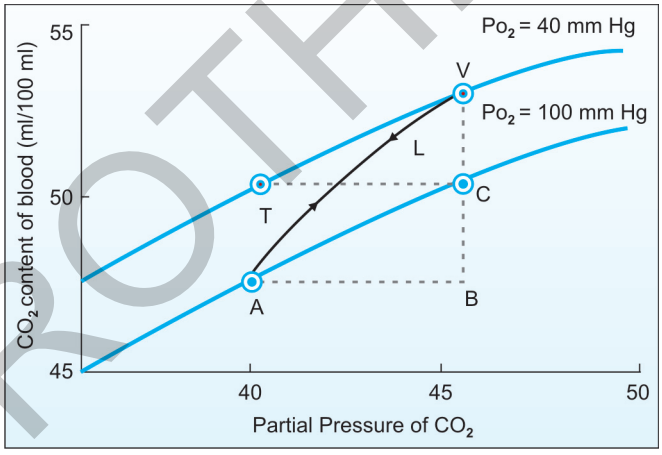

Fig. 4.3.3: The Haldane effect: the carbon dioxide dissociation curve changes with the PO_2 of blood. The diagram shows curves for PO_2 of 40 mm Hg and 100 mm Hg. The arterial blood (A) enters tissues at a PO_2 of 100 mm Hg and a PCO_2 of 40 mm Hg. Tissues have a PCO_2 of 46 mm Hg, and as a result carbon dioxide diffuses from the tissues to the blood. If this was the only process taking place in tissues, the blood carbon dioxide content would change from B to C (i.e., from 48 mL/100 mL blood to about 50 mL/100 mL). However, simultaneously the blood PO2 also falls from 100 mm Hg to about 40 mm Hg in the venous blood (V). Since the carbon dioxide dissociation curve at a PO_2 of 40 mm Hg is different, the carbon dioxide content actually changes from B to V (i.e. from 48 ml/100 ml to 52 mL/100 mL). Thus the amount of carbon dioxide picked up from tissues is doubled due to the Haldane effect. In the same way the amount of carbon dioxide released in the lungs is also doubled by the Haldane effect because the PO_2 changes simultaneously from 40 to 100 mm Hg while the PCO_2 falls from 46 to 40 mm Hg. The thick line AV represents the change in carbon dioxide content of blood that actually takes place; the arrows represent the direction of change in tissues (T) and lungs (L).

mm Hg in the tissue capillaries simultaneously with the rise in PCO_2, the CO_2 uptake is increased to 4 mL/100 mL. Thus the carbon dioxide picked up in tissues is doubled because of the effect of PO_2 on carbon dioxide dissociation curve. Haldane effect also works to our advantage when carbon dioxide is expelled in the lungs as discussed below.

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EXPULSION OF CARBON DIOXIDE

Carbon dioxide is removed from the pulmonary capillaries by diffusion. The PCO_2 of venous blood is 45 mm Hg while that of alveolar air is 40 mm Hg. Thus there is an alveolar capillary PCO_2 gradient of 5 mm Hg, which makes carbon dioxide diffuse into the alveoli till the pulmonary capillary PCO_2 falls to 40 mm Hg. Carbon dioxide is finally expelled from the alveoli during expiration.

Impact of Haldane Effect in the Lungs

While the pulmonary capillary blood is exchanging carbon dioxide with the alveoli, oxygen exchange is also going on simultaneously which raises the pulmonary capillary PO_2 from 40 to 100 mm Hg. This makes Haldane effect work in the opposite direction as compared to the tissues (Fig. 4.3.3). As seen in the figure, rise in PO_2 of the pulmonary capillary blood effectively doubles the amount of carbon dioxide eliminated from the pulmonary capillaries.

Mechanism of Haldane Effect

The mechanism of Haldane effect is intimately related to that of the Bohr effect (Chapter 4.2). Transfer of carbon dioxide from the tissues to the blood generates hydrogen ions in the RBC as discussed above. Deoxygenated haemoglobin is a better hydrogen ion acceptor than oxygenated haemoglobin. Hence, deoxygenation of haemoglobin in the tissues helps in the carriage of extra-carbon dioxide by mopping up hydrogen ions. Putting it in chemical language.

$$HbO_2 \Leftrightarrow Hb + O_2$$

Oxygen is removed by the tissues, favouring the forward reaction. Deoxygenated haemoglobin mops up hydrogen ions as follows:

$$Hb + H^+ \Leftrightarrow Hb.\ H$$

Hence, in the reversible reactions,

$$CO_2 + H_2O \hat{U} H_2CO_3 \Leftrightarrow H^+ + HCO_3^-$$

removing hydrogen ions from the scene of action promotes the forward reactions, thereby facilitating picking up of carbon dioxide. The opposite sequence of events facilitates expulsion of carbon dioxide in the lungs.

Towards the end of chapters on gas exchange and transport, you may find it interesting to reflect on the popular expressions, 'pure and impure' blood. Pure blood refers to oxygenated blood while impure blood refers to deoxygenated blood. Oxygenated blood is redder than deoxygenated blood because of the difference in the colour of the two forms of haemoglobin. But both oxygenated and deoxygenated blood carry considerable amounts of oxygen, normally 20 mL/100 mL and 15 mL/100 mL respectively. Thus the difference in the oxygen content of 'pure' and 'impure' blood is only about 25%. Besides the oxygen content, the two bloods differ also in their carbon dioxide content. Carbon dioxide is popularly considered a 'poisonous' gas, and this may justify the terms 'pure' and 'impure'. But once again, the two bloods contain 48 mL/100 mL and 52 mL/100 mL carbon dioxide respectively, the difference being only about 8 percent. If even 'pure' blood contains so much carbon dioxide, carbon dioxide can hardly be considered 'poisonous'. The arteriovenous oxygen difference is 5 mL/100 mL, and the carbon dioxide difference is 4 mL/100 mL. It means that in lungs or tissues, each 100 mL blood exchanges 5 mL oxygen and 4 mL carbon dioxide, which seems to take care of the normal resting metabolic needs. The ratio of carbon dioxide produced to oxygen consumed is thus 4/5, i.e. 0.8. The ratio is also referred to as the respiratory quotient (RQ) or respiratory exchange ratio (RER). RER is influenced by the nutrient composition of the diet as discussed in Section 7. At rest the cardiac output is about 5 L/min, i.e. 50 × 100 mL/min. Thus 50 portions of 100 mL each pass through the lungs or tissues once every minute. Since each 100 mL portion exchanges 5 mL oxygen and 4 mL carbon dioxide respectively, the oxygen consumption is 5 × 50 mL = 250 mL per min, and the carbon dioxide production is 4 × 50 mL = 200 mL per min. These are figures you will come across at many places in the book, derived in many different ways. "There is not just one way to Rome!"

QUESTION AND PROBLEM

1. Discuss the interrelationships between Bohr effect and Haldane effect.

ANSWER AND SOLUTION

1. Bohr effect describes the effect of PCO_2 on oxygen carriage, while Haldane effect describes the effect of PO_2 on carbon dioxide carriage in the blood. Both these effects depend on the properties of the haemoglobin molecule. A rise in PCO_2 generates hydrogen ions. Hydrogen ions alter the configuration of the haemoglobin molecules such that it becomes less accessible to oxygen (Bohr effect). On the other hand, deoxygenated haemoglobin combines with hydrogen ions more readily than oxyhaemoglobin (Haldane effect). Thus haemoglobin is a unique example of fine tuning at molecular level to serve a physiological function. Since oxygen has to be picked up at the same places where carbon dioxide is to be expelled, and *vice versa*, the properties of the haemoglobin molecule facilitate both these functions.

   However, quantitatively, Bohr effect is much less important than Haldane effect. While Bohr effect has only a marginal impact on oxygen carriage, Haldane effect doubles the amount of carbon dioxide transported.

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RL Bijlani
A product of the All India Institute of Medical Sciences (AIIMS), New Delhi, and the Massachusetts Institute of Technology (MIT), Cambridge, USA, Bijlani was Professor and Head of the Department of Physiology at AIIMS till he took voluntary retirement in 2005. His research work on nutrition in relation to cardiovascular disease and diabetes has been published in international journals. His other areas of expertise include medical education, history of medicine, research methodology, and yoga. In the year 2000, he established at AIIMS a patient care facility for providing lifestyle modification courses based on yoga in tune with the latest advances in mind-body medicine. He is a prolific writer, with eleven other published books to his credit. He has a pre-eminently readable writing style, and even his scientific publications have a literary flavour.

S Manjunatha
He has many firsts to his credit: the best outgoing student of Karnataka Institute of Medical Sciences, Hubli in 1995; the best postgraduate in Physiology at AIIMS, New Delhi in 2000; and one of the very few if not the only one, to have become a full professor within 10 years of completing his MD. Much loved and deeply admired by his students, Manjunatha's research interests include nutrition and other lifestyle factors in relation to chronic disease, specially diabetes mellitus, and the physiological effects and therapeutic applications of yoga.

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