Review Article

Hemoglobin and Oxygen Transport

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Abstract

Once oxygen (O_2) that is present in atmosphere enters the respiratory tract, it reaches the alveoli and diffuses from the alveoli into the pulmonary blood. It is transported to the peripheral tissue capillaries almost entirely in combination with hemoglobin (Hb). The presence of Hb in red blood cells allows the blood to transport 30–100 times as much O_2 as could be transported in the form of dissolved O_2 in blood. This article is based on the published textbooks and articles that speak on the importance of O_2 and Hb; we have tried to put it into one place so that we can relate and apply the concepts.

Key words: Anemia, carbon monoxide, hemoglobin (Hb), oxygen (O_2)

Introduction

Understanding the association between oxygen (O_2) and hemoglobin (Hb) is very much essential to manage the patients under anesthesia, critical illness, and resuscitation; the purpose of this article is to present the physical principles of O_2 in the blood and tissue fluids to understand this association.

Hemoglobin and Oxygen

Basics of oxygen transport

The O_2 delivery system in the body consists of the lungs and the cardiovascular system. O_2 delivery to a particular tissue depends on the amount of O_2 entering the lungs, the adequacy of pulmonary gas exchange, the blood flow to the tissue, and the capacity of blood to carry O_2. The blood flow depends on the degree of constriction of the vascular bed in the tissue and the cardiac output (CO). The amount of O_2 in the blood is determined by the amount of dissolved O_2, the amount of Hb in the blood, and the affinity of Hb for O_2.[1]

The primary function of blood is to transport O_2 from lungs to body tissue, carbon dioxide (CO_2) from tissue to the lungs, and hydrogen (H+) from tissue to the kidney.[2]

Normal cardiopulmonary homeostasis is a balance between gas exchange in the capillary system and the alveoli. Many factors determine this homeostasis as follows:

- Distribution of blood through capillary bed
- Arterial to venous shunts
- Cardiac output
- Metabolic rate
- Alveolar ventilation
- Partial pressure of gases.

A change in these factors may demand a change to be adopted to compensate for maintaining near normal physiological values.[2]

Previously partial pressure of O_2 (PaO_2) in arteries was used as a measure of adequate tissue oxygenation. But, even though PaO_2 certainly indicates the degree of arterial hypoxemia or hyperoxemia, direct information regarding ability of blood to deliver adequate O_2 to the tissue is not obtained from PaO_2 values alone. It also depends on the total O_2 content of the blood, chemical combining affinity of O_2 for Hb, and CO. PaO_2 determines the partial pressure gradient that is a driving force between the blood and the tissue. But, when exchange within the tissue takes place, the affinity of Hb for O_2 controls the level of PaO_2. Thereby, measuring mixed venous O_2 content gives a good indication of global tissue oxygenation and adequate tissue O_2 transport and supply.[3]

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Oxygen delivery

Global O_2 delivery (DO_2) is the amount of O_2 delivered to the whole body from the lungs. It is the product of the total blood flow or CO and the O_2 content of the arterial blood (CaO_2) and is usually expressed as mL min^{-1}.

$DO_2 = CO \times CaO_2$

Table 1 shows that in anemia with inspired O_2 of 21% and Hb of 7.5 mg%, the dissolved O_2 is 3 mL/L, Hb bound O_2 is 98 mL/L and CaO_2 is 101 mL/L; whereas with O_2 therapy with 100% O_2, PaO_2 increases to 85 mL/L and dissolved O_2 increases to 19 mL/L, Hb bound O_2 is same as in anemia and total CaO_2 is 117 mL/L. This implies with O_2 therapy there is a small change in dissolved O_2 and CaO_2.Thus improving Hb is necessary to increase CaO_2 and delivery of O_2.[4]

Oxygen consumption

Global O_2 consumption is the volume of O_2 (VO2) consumed by the tissues per minute. Under aerobic conditions, O_2 is consumed to generate energy so that VO_2 corresponds to the metabolic rate. Measurements of VO_2 are sometimes used to assess the adequacy of DO_2 on the assumption that if DO_2 is inadequate VO_2 becomes supply dependent. VO_2 can be measured directly by analysis of respiratory gases or derived from CO and arterial and venous O_2 contents. Gas analysis techniques require specialized equipment that accurately measures gas volumes and concentrations adjusting for temperature and pressure changes and other sources of inaccuracy. Calculation from CO and arterial-mixed venous O_2 content difference is simpler and can be done using a pulmonary artery catheter. The reverse/inverse Fick principle is used as follows:

$VO_2 = CO \times (CaO_2 - CVO_2)$

Factors that influence oxygen consumption and oxygen delivery

Factors increasing VO2 are surgery, trauma, burns, sepsis, inflammation, pyrexia, shivering, seizures, agitation/anxiety/pain, adrenergic drugs, and wearing from ventilation.

Factors decreasing VO_2 are starvation/hyponutrition, hypothermia/cooling, shock/hypovolemia, muscle paralysis, mechanical ventilation, antipyretics, and sedation/analgesics.

Table 1: The relative influence of anemia on oxygen delivery

Parameter	Normal	Anemic	Anemic + oxygen therapy
Inspired oxygen (%)	21	21	100
PaO_2 (kPa)	12	12	85
SaO_2 (%)	98	98	98
Hb concentration (g L^{-1})	150	75	75
Dissolved oxygen (mL L^{-1})	3	3	19
Hb-bound oxygen (mL L^{-1})	197	98	98
Total CaO_2 (mL L^{-1})	200	101	117

Oxygen extraction ratio

The O_2 extraction ratio (O_2ER) is the ratio of VO_2 to DO_2 that represents the fraction of O_2 delivered to the microcirculation that is taken up by the tissues.

$O_2ER = VO_2/DO_2$

The normal O_2ER is 0.2–0.3, indicating that only 20–30% of the delivered O_2 is utilized. This spare capacity enables the body to cope with a fall in DO_2 without initially compromising aerobic respiration and VO2. O_2ER varies between organs; the heart has a high O_2ER (~0.6) so it is particularly sensitive to reductions in coronary artery DO_2.[4]

Oxygen flux

- O_2 flux = amount of O_2 delivered to the peripheral tissues per minute
- It is the content delivered per minute and not just content (which is a volume, not vol/min)

O_2 flux = O_2 bound to Hb + dissolved O_2

O_2 bound to Hb = $CO \times [Hb] \times SO_2 \times k$

- CO = cardiac output (L/min)
- [Hb] (g/L)
- SO_2 = saturation (as fraction)
- k is Hufner's number
- Amount of O_2 that can bind with 1 g of Hb when fully saturated
- (Normal value = 1.34ml O_2/gm of Hb)
- Dissolved $O_2 = CO \times PaO_2 \times 0.03$
- PO_2 = partial pressure (mmHg)
- 0.03 mL O_2 per mmHg per L of blood can be dissolved.
- Total O_2 flux
  Arterial O_2 flux is = $5 \times 150 \times 0.98 \times 1.34 + 5 \times 100 \times 0.03$
  = 984.9 + 15
  = approx. 1000 mL O_2 per min
- Assumes CO of 5 L/min
- Assumes [Hb] = 150 g/L
- Assumes SaO_2 = 98% and PO_2 = 100 mmHg
- pH 7.4, temp = 37
  Similarly,
  Mixed venous O_2 delivery rate is
  $= 5 \times 150 \times 0.75 \times 1.34 + 5 \times 40 \times 0.03$
  = 753.75 + 6
  = 759.75
  = approx. 750 mL O_2 per min
- Assumes SVO_2 of 75% and PVO_2 of 40 mmHg.

Summary

- Total O_2 flux = 1000 mL O_2/min
- Arterial [O_2] =20 mL O_2/100 mL blood
- Mixed venous [O_2] =15 mL O_2/100 mL blood
- Normal basal consumption of O_2 = 250 mL/min.

For PaO_2 = 100 mmHg; PVO_2 = 40 mmHg or SaO_2 = 98% (or 97.5%); SVO_2 = 75%

Thus, CaO_2 = 20 mL O_2/dL; CVO_2 = 15 mL O_2/dl (approx.)

Fate of oxygen delivered to tissues

The effect of O_2 on energy is very important that is for both aerobic and anaerobic metabolism is glucose metabolism. The most familiar example of the metabolisms is glucose. The energy released is considered in terms of number of molecules of adenosine triphosphate (ATP)] formed from Adenosine diphosphate (ADP). In the presence of O_2 and the necessary enzyme (pyruvate) contained in the mitochondria, the glucose is entirely converted into CO_2 and H_2O by means of citric acid cycle. In this process, one molecule of glucose results in production of 38 molecules of ATP. Normally, ATP is dehydrolyzed to ADP, inorganic phosphate, and H+.

But in the absence of O_2, glucose is converted into lactic acid resulting in net production of only two molecules of ATP. If ATP production is inadequate for cellular activity, there is increase in lactate production. As the DO_2 falls, CO is redistributed to vital organs, O_2 extraction increases until a point at which these mechanisms become insufficient. Thus, when DO_2 is no longer adequate, anaerobic metabolism sets in and blood lactate level increases.[5] A raise in lactate level greater than 2 mEq/L suggests the possibility of inadequate tissue perfusion. Blood lactate level can be easily measured and values are same whether it is obtained from arterial or venous blood.[6] The duration of hyperlactemia may be a more sensitive indicator of outcome than a single raised lactate level in critically ill patient.[7]

Moreover, O_2 utilization is complete in the mitochondria where PO_2 must be maintained to continue aerobic metabolism above the level of Pasteur point. This is 1–2 mmHg of the PaO_2 in the atmosphere under normal circumstances. Aerobic metabolism continues at normal rate until the Pasteur point is reached, below this anaerobic metabolism sets in and reduction in ATP/ADP ratio takes place.[8]

Oxygen Cascade

O_2 cascade is the O_2 tension gradient from atmosphere to mitochondria and comprises the alternating stages of mass transport and diffusion [Figures 1, 2 and Table 2].[9]

About 98% of the blood that enters the left atrium from the lungs just passes through the alveolar capillaries and becomes oxygenated upto a PaO_2 level of about 100 mmHg. Another 2% of the blood passes from the aorta through the bronchial circulation, which supplies mainly the deep tissues of the lungs and is not exposed to lung air. This blood flow is called "shunt flow," meaning that blood is shunted past the gas exchange areas. On leaving the lungs, the PO2 of this shunt flow is about 40 mmHg. When this blood combines in the pulmonary veins with the oxygenated blood from the alveolar capillaries, this so-called venous admixture of blood causes the PO2 of the blood entering the left heart and leaving the left ventricle through the aorta to fall to about 95 mm Hg.[10]

Here, the basic Pulmonary gas Equation is,

$PaO_2 = 21\% (P_B - P_{H2O}) - PaCO_2/R$

where PaO_2 = partial pressure of O_2

P_B = atmospheric pressure = 760 mmHg
P_{H2O} = partial pressure humidity = 47 mmHg
$PaCO_2$ = partial pressure of CO_2 = 45 mmHg
R = respiratory quotient

Now, applying this equation,

a) PaO_2 in atmosphere
$PaO_2 = 21\% (P_B) = 21\% (760) = 159$ mmHg

b) PaO_2 in presence of humidity
$PaO_2 = 21\% (P_B - P_{H2O}) = 21\% (760 - 47) = 149$ mmHg

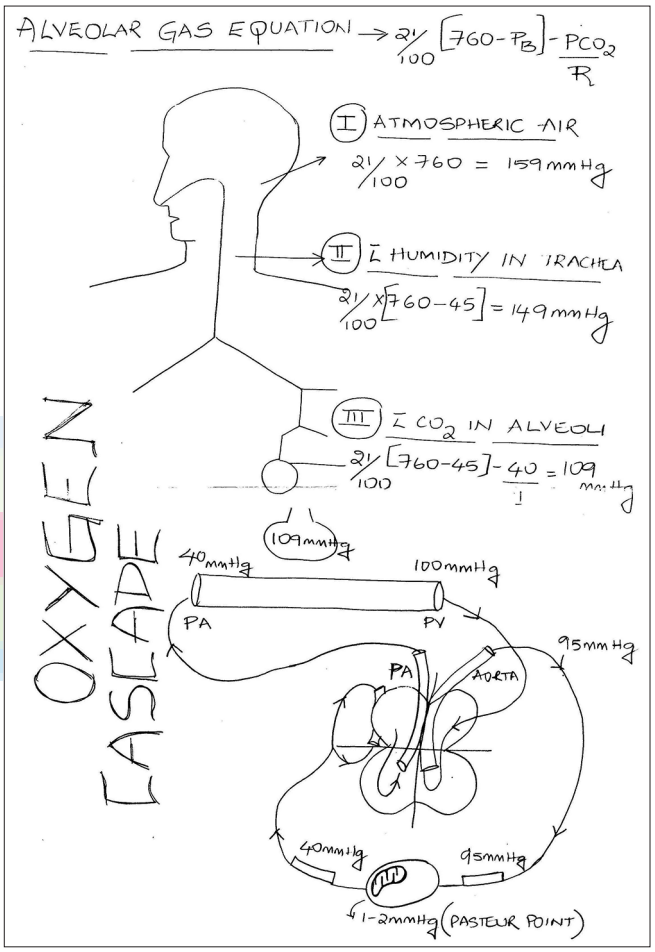

Figure 1: Depicting oxygen cascade (adapted from: Guyton AC. Textbook of Medical Physiology. Philadelphia, Pennsylvania: Elsevier Inc.; 2006;11 (40):503.)

Table 2: This table depicts different partial pressure gradients along the respiratory tract of oxygen, carbon dioxide, and nitrogen

mmHg	Trachea	Alveoli	Arterial blood	Mixed venous blood
PO_2	149.2	104	100	40
PCO_2	O.3	40	40	46
P_{H2O}	47	47	47	47
PN_2	563.5	569	573	573
Total	760	760	760	706

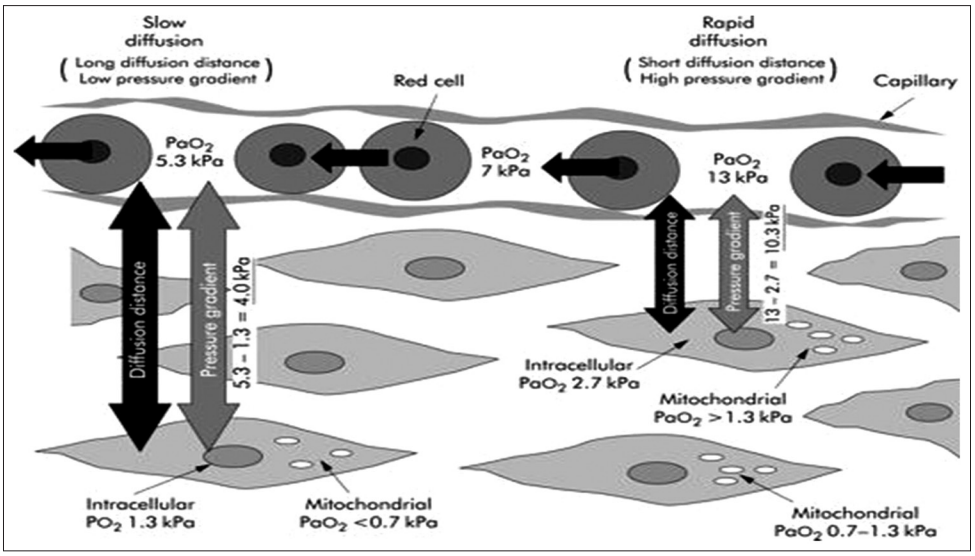

Figure 2: Diagram showing the importance of local capillary oxygen tension and diffusion distance in determining the rate of oxygen delivery and the intracellular PO_2. On the left there is a low capillary PO_2 and pressure gradient for oxygen diffusion with an increased diffusion distance resulting in low intracellular and mitochondrial PO_2. On the right, the higher PO_2 pressure gradient and the shorter diffusion distance result in significantly higher intracellular PO_2 values

c) PaO_2 in presence of CO_2
$PaO_2 = 21\% (P_B - P_{H2O}) - PaCO_2/R$
$= 21\% (760 - 47) - 45/1$
$= 109$ mmHg

Also in the end of the above diagram, we can see that only 1 – 3 mmHg of O_2 pressure is required for the full support of the chemical processes that use O_2 in the cell. Below this point in mitochondria, there occurs transition from aerobic to anaerobic respiration that is called "Pasteur point." In Figure 2, on the left there is a low capillary PO_2 and pressure gradient for oxygen diffusion with an increased diffusion distance resulting in low intracellular and mitochondrial PO_2. On the right, the higher PO_2 pressure gradient and the shorter diffusion distance result in significantly higher intracellular PO_2 values.

It is always said that the sum of the partial pressure of gases must be equal to the barometric pressure.

Oxy–Hemoglobin

Hb is a protein made up of four subunits, each of which contains a heme moiety attached to a polypeptide chain. In normal adults, most of the Hb molecules contain two alpha and two beta chains. Heme is a complex made up of a porphyrin and one atom of ferrous iron. The iron stays in the ferrous state, so that the reaction is an oxygenation, not an oxidation.

The quaternary structure of Hb determines its affinity for O_2. In deoxy Hb, the globin units are tightly bound in a tense (T) configuration that reduces the affinity of the molecule for oxygen. When O_2 is first bound, the bonds holding the globin units are released, producing a relaxed (R) configuration that exposes more oxygen binding sites. The net result is a 500-fold increase in O_2 affinity.[1]

Oxyhemoglobin dissociation curve

The oxygen–Hb dissociation curve, [Figures 3 and 4] the curve relating percentage saturation of the O_2-carrying power of Hb to the PO_2, has a characteristic sigmoid shape.[11] It is because, combination of the first heme in the Hb molecule with O_2 increases the affinity of the second heme for O_2, and oxygenation of the second heme increases the affinity of the third heme for O_2, and so on, so that the fourth heme molecule for oxygen is many times than that for the first heme molecule.[1]

P_{50}—it is the PaO_2 at which there is 50% saturation of Hb with O_2.

$P_{50} = 27$ mmHg/3.6 kPa

There are some factors that shift oxyHb curve to right and left. They are described in the figure given later in this article.

Anemia, carbon monoxide poisoning, and methemoglobinemia

In anemia, it is important to realize that to meet the O_2 [Figures 5 and 6] delivery [DO_2] and O_2 consumption [VO_2], decrease in any one of the variables, that is, CO, O_2 saturation, and Hb saturation, there will be a decrease in the amount of O_2 available to the tissue leading on to hypoxia.[11]

PO_2 versus O_2 content in carbon monoxide poisoning and anemia

In carbon [Figure 6] monoxide poisoning, abnormal shift of the curve occurs, which is very important in clinical practice.[11] CO combines with Hb very rapidly and form carboxy-Hb (Hb-CO). This has an affinity of about 210 times greater than O_2. Hb-CO not only displaces O_2 but also it shifts the curve to the left. At 50% concentration of Hb-CO, P_{50} is reduced to 14 mmHg, leading on to very dangerous level of hypoxia. There is a need to ventilate with 100% O_2 or with hyperbaric O_2.[12]

PO_2 versus O_2 content in methemoglobinemia poisoning and anemia

In methemoglobinemia poisoning, the binding of O_2 to methemoglobin results in an increased affinity of O2 to the three other heme sites (that are still ferrous) within the same tetrameric hemoglobin unit. This leads to an overall reduced

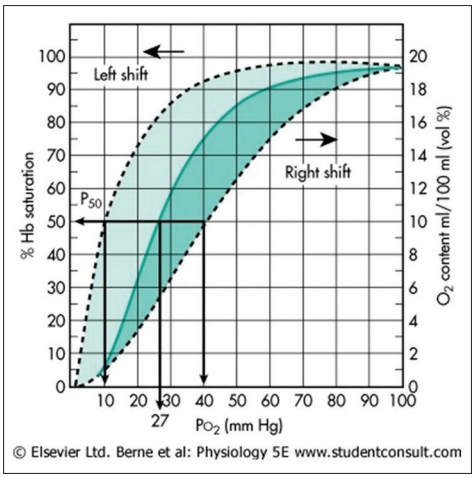

Figure 3: Oxyhemoglobin dissociation curve

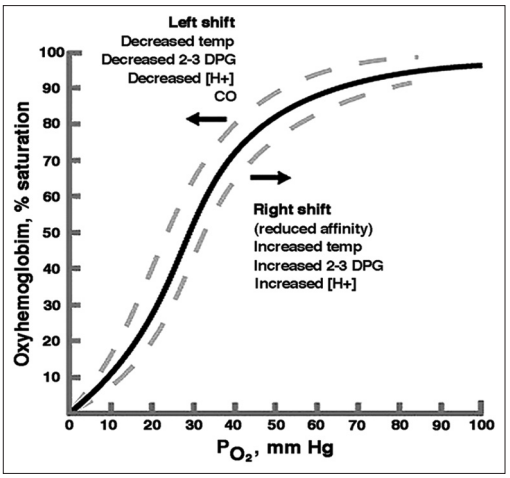

Figure 4: Oxyhemoglobin dissociation curve

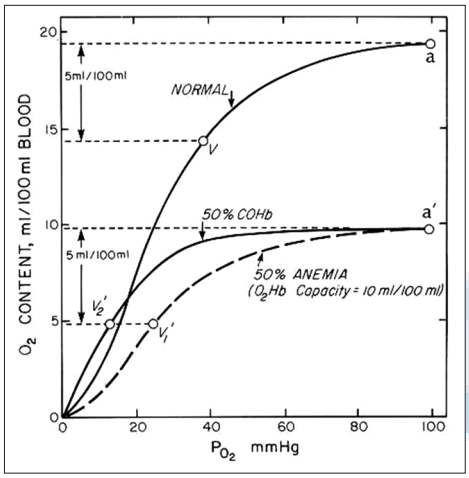

Figure 5: Influence of anemia and carbon monoxide on oxyhemoglobin dissociation curve

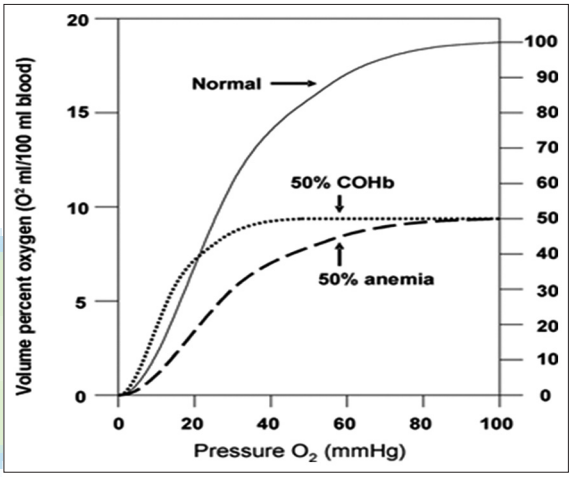

Figure 6: Effect of Carboxy-hemoglobin on oxyhemoglobin dissociation curve

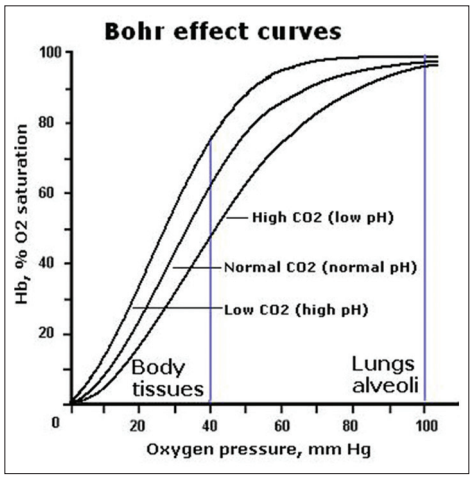

Figure 7: Bohr effect curves (Adapted from: Ganong WF. Review of Medical Physiology. Lange and McGraw Hill 2005;22 (35):667)

ability of the red blood cell to release O_2 to tissues, with the associated O_2–Hb dissociation curve therefore shifted to the left. When methemoglobin concentration is elevated in red blood cells, tissue hypoxia can occur.[11]

Bohr effect and double Bohr effect

A shift of the O_2–Hb dissociation curve [Figure 7] to the right in response to the increase in blood carbon dioxide and hydrogen ions has a significant effect by enhancing the release of O_2 from the blood in the tissues and enhancing oxygenation of blood in the lungs. This is called Bohr effect, which can be explained as follows: As the blood passes through the tissues, carbon dioxide diffuses from the tissue cells into the blood. This increases the blood PO_2, which in turn raises the blood H_2CO_3 (carbonic acid) and the hydrogen ion concentration. These effects shift the O_2–Hb dissociation curve to the right and thereby delivering increase amount of O_2 to tissues.[13]

Double Bohr Effect

When the Bohr shift operates in one direction in the maternal blood and in other direction in the fetal blood, this phenomenon is called double Bohr effect.

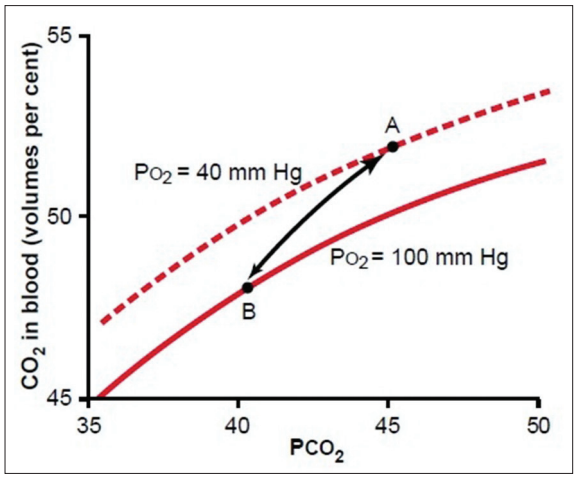

Figure 8: Haldane effect curves (Adapted from: Guyton and Hall. Text book of Medical Physiology. Elsevier Saunders 2006;11 (40):512.)

Reverse Bohr Effect

The affinity of hemocyanin (A metallorespiratory protein) toward O_2 due to decrease in pH in certain invertebrates leads to the occurrence of an effect in which accumulation of lactate in the blood is established. This effect is called reserve Bohr effect.

Haldane effect and double Haldane effect

Increase in the concentration of carbon dioxide will [Figure 8] displace O_2 from Hb and binding of O_2 with Hb in turn will displace carbon dioxide from blood. This phenomenon is referred to as the Haldane effect.[14]

Double Haldane effect

Mostly prominent in the intrauterine life, the Haldane effect takes places in the uteroplacental circulation in which the affinity of fetal carbon dioxide decreases and the uptake of maternal carbon dioxide is enhanced. As the intake of O_2 in fetal blood takes place, the release of carbon dioxide becomes more likely. The double Haldane effect accounts for approximately 46% of the transplacental carbon dioxide transfer.

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Conflicts of interest

There are no conflicts of interest.

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