# ***Minireview Article***

## Oxygen Dissociation Curve: Its Physiology and Influencing Factors

**ABSTRACT:** The oxyhemoglobin dissociation curve is a vital tool for comprehending how blood transports and releases oxygen. Oxygen is carried throughout the body both in bound form with protein (hemoglobin present inside RBC) and dissolved in blood plasma. The oxyhemoglobin dissociation curve helps to describe the relationship of oxygen saturation ($SaO_2$) i.e. percentage of oxygen bound to oxygen and partial pressure of oxygen in the blood ($PaO_2$).[1]

***Keywords:*** *Oxygen dissociation curve, oxygen binding affinity, Bohr effect*

## INTRODUCTION:

Oxygen saturation is essential for medical care and is closely regulated within the body.[2] Most oxygen (98%) transported within the body is attached to the hemoglobin, whereas a small fraction (2%) is in dissolved form in the blood [17-19]. At atmospheric pressure, oxygen in dissolved form is only 3ml per liter per Henry's law, whereas approximately 197 ml of $O_2$ per liter is transported in protein-bound form. That means the dissolved fraction contributes a minor portion to the total amount of oxygen carried in the bloodstream.[3, 4,20,21.]

Concerning oxygen transport in the bloodstream, we need to understand two terms, (i) Oxygen saturation ($SaO_2$) means the percentage of hemoglobin bound to Oxygen and Partial pressure of oxygen in the blood ($PaO_2$) and this determines the amount of Oxygen dissolved in blood.

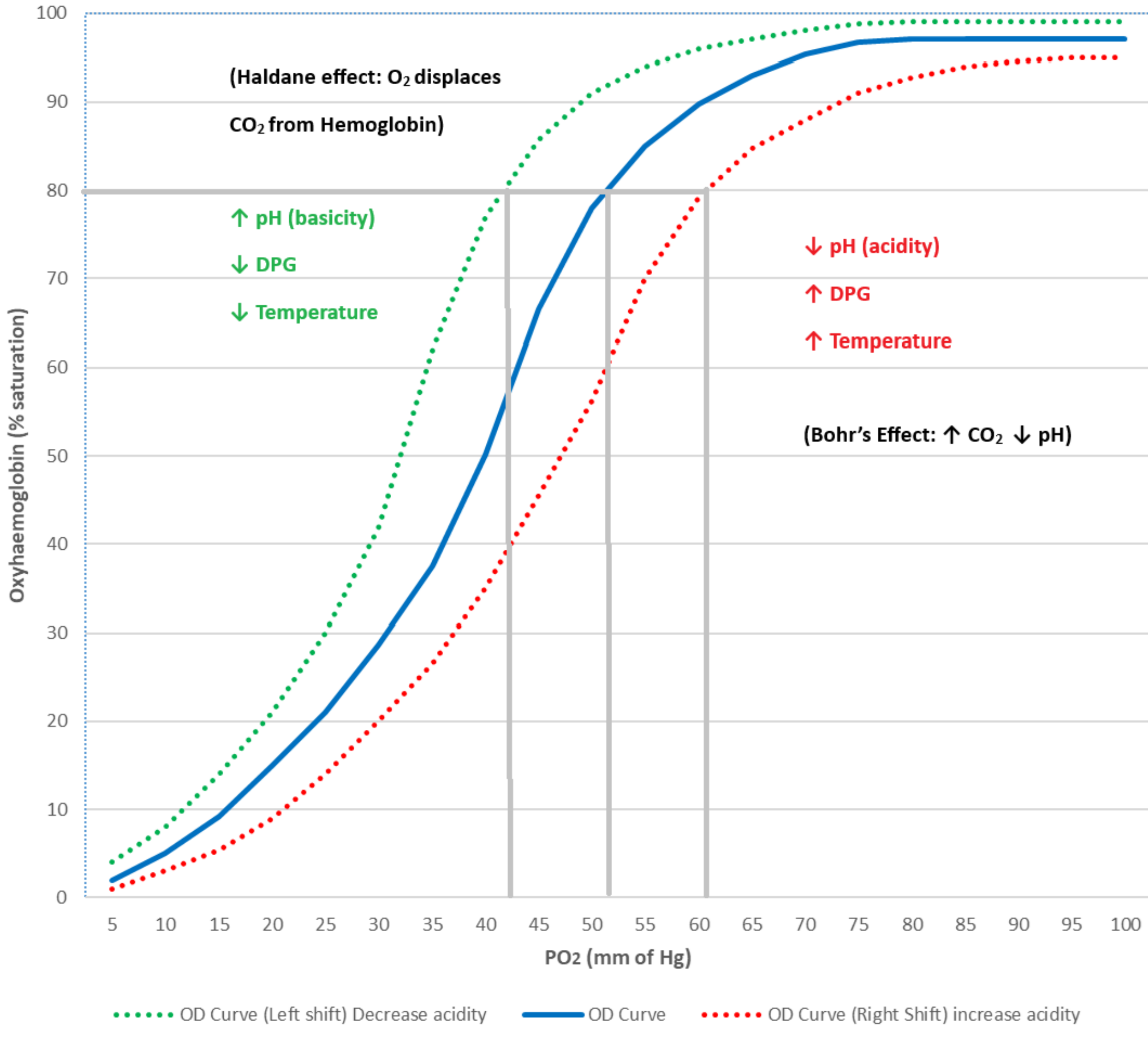
## DISCUSSION:

Hemoglobin has two parts namely a protein part (Globin) and a non-protein part (haem). This haem is composed of 4 subunits (2 alpha and 2 beta) bound to an iron atom which is in ferrous form (Fe++). This hemoglobin tetramer binds to 4 Oxygen molecules.[5]

In general, the Oxygen dissociation curve is a sigmoid curve. The curve is obtained by plotting oxygen tension on the X-axis and hemoglobin saturation on the Y-axis. It gives a visual impression of how oxygen binds to hemoglobin.

Many physiologic factors can shift the oxygen dissociation curve either to the right or the left. Shift to the right causes hemoglobin to have a lesser affinity for oxygen and causes easier unloading of oxygen from hemoglobin. The shift to the left increases the affinity of hemoglobin for oxygen and causes hemoglobin to take up and retain oxygen more readily. An increase in carbon dioxide, increase in hydrogen ion (i.e. decreased pH or acidity), increase in 2,3-DPG, and an increase in temperature shifts the curve rightwards.

Hemoglobin exists in two states, the T state (tense, low affinity, deoxygenated) and the R state (relaxed, high affinity, oxygenated). These two states differ in their oxygen-binding affinity. In the unbound form, hemoglobin subunits exist in the T state. In lung alveoli, where there is a higher partial pressure of oxygen ($pO_2$), a hemoglobin subunit in the T state binds oxygen causing a conformational change in the other hemoglobin subunits, changing them to high-affinity R state. This causes oxygen binding to occur with ease. This process, in which one hemoglobin subunit helps others to gain more affinity for oxygen is termed as positive cooperativity.[6, 7.]




**<u>Figure 1</u>: Hemoglobin Dissociation Curve:** The dotted line corresponds with the shift to the right caused by Bohr effect.

### *Parameters affecting Oxygen dissociation curve.*

**pH:** With the increase of hydrogen ions acidity increases (or pH decrease). So, a decrease in pH (acidity) shifts the dissociation curve rightwards. The opposite is also true. An increase in pH (alkalinity) shifts the dissociation curve to the left.[8]

**Carbon Dioxide:** The effect of carbon dioxide and H+ ions on the oxygen dissociation curve is quite closely related. Carbon dioxide is mostly transported in the blood bloodstream in the bicarbonate buffer system, with a small portion being transported in carbaminohemoglobin form. Carbon dioxide on entering the red blood cells quickly converts to carbonic acid with the help of the enzyme carbonic anhydrase. This acid immediately dissociates into bicarbonate and hydrogen ion (H+ ion). The increase in hydrogen ion shifts the dissociation curve to the right by stabilizing the hemoglobin in the T-state, weakening its binding capacity, and increasing the likelihood of dissociation thus promoting the oxygen unloading. Hemoglobin's lower affinity for oxygen secondary to increases in the partial pressure of carbon dioxide is called the Bohr effect.[9, 10, 11.]

**2, 3-Diphosphoglycerate (DPG):** At high altitudes where the oxygen level is low, hyperventilation occurs causing $CO_2$ washout, less $pCO_2$, and less hydrogen ion concentration leading to leftward shifting of oxygen-hemoglobin dissociation curve. As a counter mechanism, the red blood cells produce more 2, 3-DPG which leads to the shifting of the curve to its normal position i.e. rightwards and establish a respiratory compensation state. That means under the stress of chronic hypoxic conditions at high altitudes, more 2,3-DPG is produced, which shifts the oxy-hemoglobin dissociation curve to the right in favor of oxygen unloading. The relationship of hydrogen ions is inversely proportionate with levels of 2, 3 DPG.[12, 13, 14.]

**Temperature:** Oxygen unloading is favored with a rightward shift of the curve as the temperature increases. Exercise is an example. Muscular temperature increases with increased exercise, shifting the curve to the right, and creating an environment where more and more oxygen is available for utilization as per the tissue demand.[15]

**Carbon monoxide:** Carbon monoxide has 240 times more affinity for hemoglobin than oxygen. Therefore, during carbon monoxide poisoning, CO attaches tightly with hemoglobin (carboxyhemoglobin), causing structural changes in the other oxygen binding sites of hemoglobin to relax (R) stage, and causing more affinity for oxygen and a leftward shift of curve. Therefore, the unloading of oxygen in the peripheral tissue is hampered. Despite maintaining normal $paO_2$, the person faces a state of tissue hypoxia. As the pulse oximeter is unable to differentiate carboxyhemoglobin from oxyhemoglobin, the person seems to be normal as per the reading of this machine.[1]

**Fetal Hemoglobin:** Fetal hemoglobin (HbF) is composed of 2 alpha and 2 gamma chain proteins in contrast to the adult hemoglobin (HbA) which is made up of 2 alpha and 2 beta chain. Due to this structural difference, fetal hemoglobin has a higher affinity for oxygen. The partial pressure at which HbF is half saturated with oxygen (P50) is 19 mm Hg, compared to 27 mm Hg for HbA. This helps the easier extraction of oxygen from maternal circulation for the fetus.[16]

## CONCLUSION:

The oxyhemoglobin dissociation curve is a vital tool for comprehending how blood transports and releases oxygen. Detail knowledge of various factors involved in the right and the left shift of the oxygen-hemoglobin dissociation curve is essential for understanding the different physiological processes that occur at the tissue level and the level of the alveoli.

**CONFLICT OF INTEREST:** None

## DISCLOSURE STATEMENT

Author Arijit Sil is an employee of IQVIA, a leading global provider of advanced analytics, technology solutions, and clinical research services to the life sciences industry but the views in the article are the author's own. Other than this, the author declares no professional, academic, competitive, or financial conflicts of interest related to this article. No funding was used in the preparation of this article.

## COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.



## REFERENCES

1. Patel S, Jose A, Mohiuddin SS. Physiology, Oxygen Transport and Carbon Dioxide Dissociation Curve. [Updated 2023 Mar 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539815/. Accessed October 27, 2024
2. Abraham EA, Verma G, Arafat Y, Acharya S, Kumar S, Pantbalekundri N. (July 25, 2023) Comparative Analysis of Oxygen Saturation by Pulse Oximetry and Arterial Blood Gas in Hypoxemic Patients in a Tertiary Care Hospital. Cureus 15(7): e42447. Doi: 10.7759/cureus.42447
3. Kaufman DP, Kandle PF, Murray IV, et al. Physiology, Oxyhemoglobin Dissociation Curve. [Updated 2023 Jul 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499818/. Accessed October 27, 2024
4. Hess W. Die Sauerstoffaffinität des Hämoglobins--ihre Bedeutung unter physiologischen und pathologischen Bedingungen [Affinity of oxygen for hemoglobin--its significance under physiological and pathological conditions]. Anaesthesist. 1987 Sep;36(9):455-67. German.
5. Thom CS, Dickson CF, Gell DA, Weiss MJ. Cold Spring HarbPerspect Med 2013;3:a011858. DOI: 10.1101/cshperspect.a011858
6. Cambronero JG. The oxygen dissociation curve of hemoglobin: bridging the gap between biochemistry and physiology. J Chem Educ. 2001 Jun; 78(6): 757. doi: 10.1021/ed078p757
7. Mihailescu MR, Russu IM. A signature of the T ---> R transition in human hemoglobin. Proc Natl Acad Sci U S A. 2001; 98(7):3773-7. doi: 10.1073/pnas.071493598.
8. Sharan M, Popel AS. Algorithm for computing oxygen dissociation curve with pH, PCO2, and CO in sheep blood. J Biomed Eng. 1989 Jan;11(1):48-52. doi: 10.1016/0141-5425(89)90165-9
9. Malte H, Lykkeboe G. The Bohr/Haldane effect: a model-based uncovering of the full extent of its impact on O2 delivery to and CO2 removal from tissues. J Appl Physiol. 2018; 125(3): 916-922. doi: 10.1152/japplphysiol.00140.2018

10. Benner A, Patel AK, Singh K, Dua A. Physiology, Bohr Effect. 2023 Aug 8. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. Available from: https://pubmed.ncbi.nlm.nih.gov/30252284/. Accessed October 27, 2024
11. Malte H, Lykkeboe G, Wang T. The magnitude of the Bohr effect profoundly influences the shape and position of the blood oxygen equilibrium curve. Comp Biochem Physiol A Mol Integr Physiol. 2021 Apr;254:110880. doi: 10.1016/j.cbpa.2020.110880.
12. Sohmer PR, Dawson RB. The significance of 2,3-DPG in red blood cell transfusions, Review CRC Crit Rev Clin Lab Sci. 1979;11(2):107-74.doi: 10.3109/10408367909105855
13. Scott AV, Nagababu E, Johnson DJ. 2,3-Diphosphoglycerate Concentrations in Autologous Salvaged Versus Stored Red Blood Cells and in Surgical Patients After Transfusion. Anesthesia Analgesia. 2016; 122(3): 616-23
14. Mairbäurl H, Schobersberger W, Hasibeder W, Schwaberger G, Gaesser G, Tanaka KR. Regulation of red cell 2,3-DPG and Hb-O2-affinity during acute exercise. Eur J Appl Physiol Occup Physiol. 1986;55(2):174-80. doi: 10.1007/BF00715001
15. Woyke S, Brugger H, Ströhle M et al. Effects of Carbon Dioxide and Temperature on the Oxygen-Hemoglobin Dissociation Curve of Human Blood: Implications for Avalanche Victims. Front Med (Lausanne). 2022 Feb 7; 8:808025. doi: 10.3389/fmed.2021.808025
16. Kaufman DP, Khattar J, Lappin SL. Physiology, Fetal Hemoglobin. 2023 Mar 20. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. Available from: https://pubmed.ncbi.nlm.nih.gov/29763187/. Accessed October 27, 2024
17. Boening, D., Kuebler, W. M., & Bloch, W. (2021). The oxygen dissociation curve of blood in COVID-19. *American journal of physiology-lung cellular and molecular physiology*. 321: L349–L357, 2021
18. Rengasamy, S., Nassef, B., Bilotta, F., Pugliese, F., Nozari, A., & Ortega, R. (2021). Administration of supplemental oxygen. *New England Journal of Medicine*, *385*(3), e9.
19. Balcerek, B., Steinach, M., Lichti, J., Maggioni, M. A., Becker, P. N., Labes, R., ... & Fähling, M. (2020). A broad diversity in oxygen affinity to haemoglobin. *Scientific reports*, *10*(1), 16920.
20. Sun, H., Wang, M., Zhang, S., Liu, S., Shen, X., Qian, T., ... & Yan, C. (2021). Boosting oxygen dissociation over bimetal sites to facilitate oxygen reduction activity of zinc-air battery. *Advanced Functional Materials*, *31*(4), 2006533.
21. Ishihara, A., Nagatomo, F., Fujino, H., & Kondo, H. (2014). Exposure to Mild Hyperbaric Oxygen Increases Blood Flow and Resting Energy Expenditure but not Oxidative Stress. *Journal of Scientific Research and Reports,* 3(14), 1886–1896.