

*Mechanisms of Disease*FRANKLIN H. EPSTEIN, M.D., *Editor***RESPIRATORY FUNCTION
OF HEMOGLOBIN**

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HEMOGLOBIN is essential for oxygen transport, and the study of its structure and function has led to numerous discoveries that have shaped modern biologic science.¹ This review will examine how hemoglobin actively regulates oxygen transport and will illustrate the clinical and physiologic importance of this regulation.

OXYHEMOGLOBIN DISSOCIATION CURVE

The oxyhemoglobin dissociation curve describes the relation between the oxygen saturation or content of hemoglobin and the oxygen tension at equilibrium. Bohr^{2,3} first showed that the dissociation curve was sigmoid-shaped, leading Hill⁴ to postulate that there were multiple oxygen-binding sites on hemoglobin and to derive an empirical approximation of the relation:

$$\left(\frac{\text{oxygen tension}}{P_{50}}\right)^n = \frac{\text{oxygen saturation}}{100 - \text{oxygen saturation}}$$

where P_{50} is the oxygen tension (in millimeters of mercury) when the binding sites are 50 percent saturated. Within the range of saturation between 15 and 95 percent, the sigmoid shape of the curve can be described by the Hill coefficient ($n = 2.7$; range, 2.4 to 2.9), and its position along the oxygen-tension axis can be described by the P_{50} , which is inversely related to the binding affinity of hemoglobin for oxygen. The P_{50} can be estimated by measuring the oxygen saturation of blood equilibrated to different levels of oxygen tension, correcting to standard conditions (37°C, pH 7.40, and carbon dioxide tension of 40 mm Hg), and fitting the results to a straight line in logarithmic form to solve for P_{50} . The

resulting standard P_{50} (normally, 26.3 mm Hg in adults at sea level) is useful in detecting abnormalities in the affinity of hemoglobin for oxygen resulting from hemoglobin variants or from disease. However, the important physiologic effects are determined by the in vivo P_{50} , which changes rapidly in response to changes in body temperature, carbon dioxide tension, and pH. In vivo P_{50} can be estimated from standard P_{50} by applying appropriate corrections to the Hill equation^{5,6} or by using a computer subroutine.⁷

Structure-Function Relations

Normal adult hemoglobin (molecular weight, 64,500) consists of two α and two β polypeptide chains, each bound to a heme group. Each heme group contains a porphyrin ring and a ferrous atom capable of reversibly binding one oxygen molecule.⁴ The globin units of deoxyhemoglobin are tightly held by electrostatic bonds in a tense (T) conformation with a relatively low affinity for oxygen. Binding of oxygen imposes chemical and mechanical stresses that break these electrostatic bonds, leading to a relaxed (R) conformation in which the remaining binding sites become more exposed and have an affinity for oxygen that is 500 times as high as when the molecule is in the T conformation.⁸ Conformational changes lead to cooperativity among binding sites, so that binding of one oxygen molecule to deoxyhemoglobin increases the oxygen affinity of the remaining binding sites on the same hemoglobin molecule. Thus, the binding curve assumes a sigmoid shape, reflecting the transition from low to high affinity as more binding sites become occupied.⁴ This cooperativity during oxygen transport provided the first clear insight into how an allosteric enzyme regulates a metabolic pathway.⁹ The properties of an allosteric protein include multiple interacting binding sites, reversible noncovalent binding to a primary ligand, quaternary conformational changes induced by ligand binding (homotropic effects), and modulation of ligand binding by secondary effectors (heterotropic effects).¹⁰ The major heterotropic effectors of hemoglobin are hydrogen ion, carbon dioxide, and red-cell 2,3-bisphosphoglycerate.

Hydrogen Ion and Oxygen-Carbon Dioxide Coupling

Adding hydrogen ion or carbon dioxide to blood reduces the oxygen-binding affinity of hemoglobin; this is known as the Bohr effect (Fig. 1A).³ Conversely, oxygenation of hemoglobin reduces its affinity for carbon dioxide; this is known as the Haldane effect (Fig. 1B).¹¹ These effects arise from interac-

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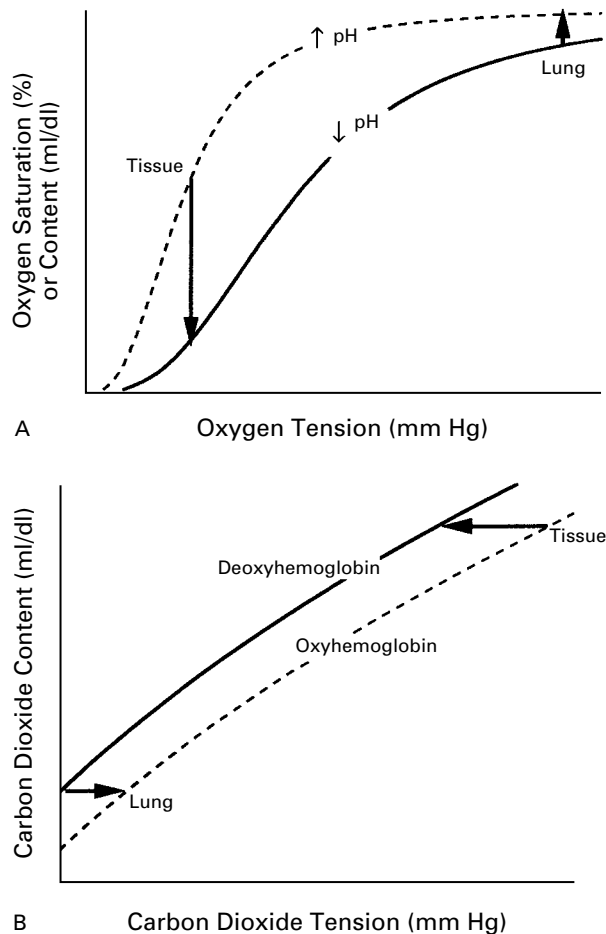


Figure 1. Reciprocal Interactions between Oxygen and Carbon Dioxide Binding to Hemoglobin.

Panel A shows the Bohr effect: binding of carbon dioxide to hemoglobin reduces the pH and the binding affinity of hemoglobin for oxygen, leading to a higher P_{50} . Panel B shows the Haldane effect: binding of oxygen to hemoglobin reduces its binding affinity for carbon dioxide, leading to a rightward shift of the carbon dioxide dissociation curve. These interactions work in opposite directions in the lungs and peripheral tissues to maximize the difference in arteriovenous oxygen content (Panel A) and minimize the difference in arteriovenous carbon dioxide tension (Panel B).

tions among oxygen, hydrogen ion, and carbon dioxide bound to different sites on hemoglobin. In the tissue capillaries, carbon dioxide can diffuse as a dissolved gas, bind to the α -amino terminus of the globin chain as carbaminohemoglobin, or be hydrated by the action of carbonic anhydrase to form bicarbonate (Fig. 2). The hydrogen ions released by the latter two reactions bind to specific amino acid residues on the globin chain to stabilize the T conformation and facilitate the release of oxygen (the acid Bohr effect).^{4,12} Carbaminohemoglobin itself

can also directly stabilize the T conformation (the carbon dioxide Bohr effect). Deoxyhemoglobin, in turn, increases the uptake of carbon dioxide by favoring the formation of bicarbonate and carbaminohemoglobin (the Haldane effect).¹³⁻¹⁵ About 80 percent of the output of carbon dioxide from tissue is transported as bicarbonate, 10 percent as carbaminohemoglobin, and 10 percent in physical solution.^{16,17}

As blood passes through the tissue capillaries, the uptake of carbon dioxide by red cells raises the oxygen tension of oxyhemoglobin at a given oxygen saturation by means of the Bohr effect, thereby facilitating the unloading of oxygen (Fig. 1A, tissue arrow). The unloading of oxygen lowers the carbon dioxide tension inside the red cells at a given carbon dioxide content by means of the Haldane effect, thereby facilitating the uptake of carbon dioxide (Fig. 1B, tissue arrow). The reverse occurs in pulmonary capillaries, as illustrated by the opposite directions of the corresponding lung arrows in Figure 1. These rapid interactions between the Bohr and Haldane effects promote the optimal transport of both oxygen and carbon dioxide by red cells, particularly during exercise. The net effects are to maximize the difference in oxygen content between arterial and venous blood and to minimize both the difference in carbon dioxide tension between arterial and venous blood and tissue acidosis. Up to 40 percent of the exchange of carbon dioxide in the tissues and 20 percent of the exchange of oxygen in the tissues can be attributed to these coupled oxygen-carbon dioxide transport mechanisms.¹³

Red-Cell 2,3-Bisphosphoglycerate

Red-cell metabolism depends solely on glycolysis, and 2,3-bisphosphoglycerate is a normal metabolic intermediate (Fig. 3). Usually, 1,3-bisphosphoglycerate is converted to 3-phosphoglycerate, producing one ATP molecule. 1,3-Bisphosphoglycerate can also be converted to 2,3-bisphosphoglycerate by bisphosphoglycerate synthase through a minor pathway without producing ATP. In most cells, the concentration of 2,3-bisphosphoglycerate is very low, because of potent feedback inhibition of bisphosphoglycerate synthase. However, in red cells, 2,3-bisphosphoglycerate becomes sequestered by binding to deoxyhemoglobin; without the normal inhibition, 2,3-bisphosphoglycerate accumulates in high concentrations.¹⁸

The binding of 2,3-bisphosphoglycerate in an electrically charged pocket between the β chains of hemoglobin stabilizes the T conformation and reduces its affinity for oxygen.^{4,18} The binding of 2,3-bisphosphoglycerate also lowers the intracellular pH and further enhances the Bohr effect. The P_{50} increases directly with the 2,3-bisphosphoglycerate concentration,¹⁹ which increases whenever the availabil-

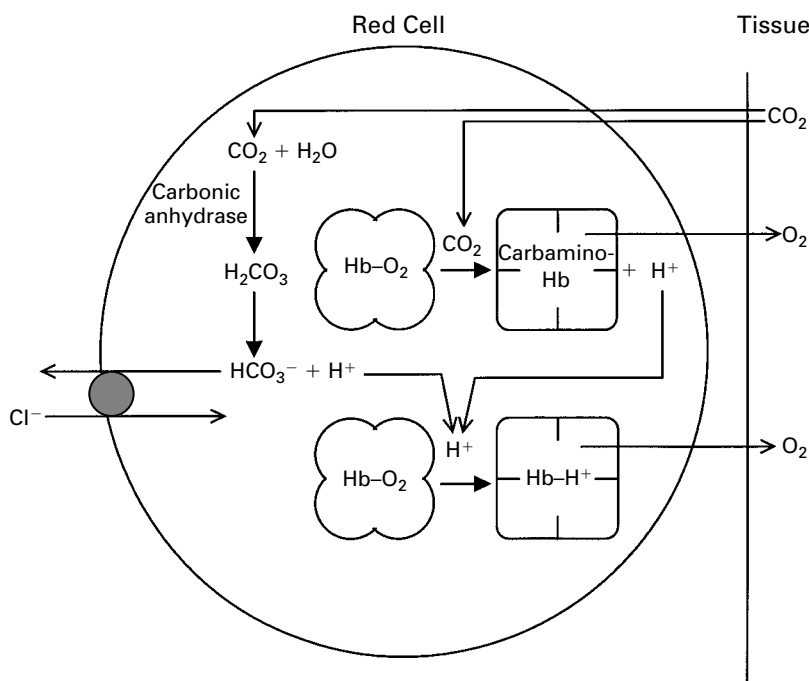


Figure 2. Coupled Oxygen and Carbon Dioxide Transport within the Red Cell.

In the peripheral tissues, the uptake of carbon dioxide by red cells and chemical reactions with hemoglobin facilitate the release of oxygen from hemoglobin. Hb denotes hemoglobin.

ity of oxygen is diminished (as in hypoxia or anemia) or the flux through glycolysis is stimulated (as in alkalosis). The 2,3-bisphosphoglycerate concentration is reduced in aging red cells and under conditions of hyperoxia or inhibition of glycolysis (by acidosis or hypophosphatemia). Other organophosphates and anions, such as chloride, also compete with 2,3-bisphosphoglycerate for binding sites on hemoglobin. Hence, their presence can reduce the regulatory effect of 2,3-bisphosphoglycerate on oxygen affinity.¹⁰

Effect of Temperature

As the body temperature increases, the affinity of hemoglobin for oxygen decreases, raising the P_{50} and facilitating oxygen release. This feature is particularly beneficial during prolonged heavy exercise. Temperature effects can cause errors in the interpretation of blood gas values, because in clinical laboratories the oxygen tension is usually measured at 37°C, not at the temperature in vivo. Hence, the true in vivo oxygen tension may be underestimated in hyperthermia and overestimated in hypothermia, particularly when the oxygen tension lies along the steep portion of the dissociation curve.⁶ For example, in a febrile patient (temperature, 41°C) with a measured arterial oxygen tension of 60 mm Hg (at

37°C), the true in vivo oxygen tension is approximately 20 percent higher (72 mm Hg). The same measurement in a patient with hypothermia (temperature, 33°C) corresponds to an in vivo oxygen tension of approximately 48 mm Hg. The carbon dioxide tension is similarly underestimated in hyperthermia and overestimated in hypothermia. Correction for these temperature effects permits the accurate calculation of the alveolar-arterial oxygen tension gradient. Since the pH of neutrality varies with temperature, no correction for pH is necessary. These corrections are available in nomograms or computer algorithms.⁵

Binding of Nitric Oxide

Hemoglobin scavenges nitric oxide through the high-affinity ferrous binding sites on heme (with an affinity for nitric oxide 8000 times their affinity for oxygen). Recently a second binding site was reported at the $\beta 93$ cysteine residue on the globin chain, where nitric oxide binds in the form of *S*-nitrosothiol.²⁰ The transfer of nitric oxide from *S*-nitrosothiol to hemoglobin is allosterically regulated and functionally linked to the binding of oxygen to hemoglobin. As hemoglobin binds oxygen in the lungs, its binding affinity for *S*-nitrosothiol is increased. As

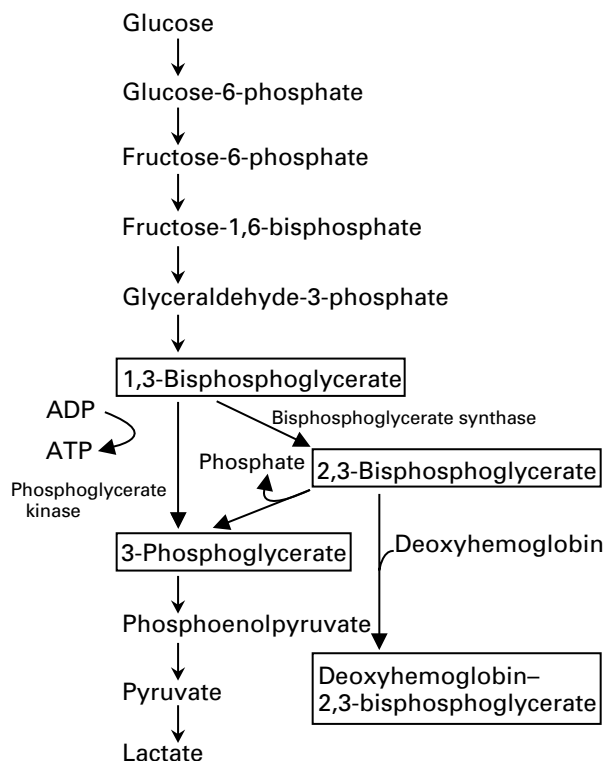


Figure 3. Glycolysis in Red Cells.

The intermediate compound 2,3-bisphosphoglycerate is sequestered by binding to deoxyhemoglobin; hence, feedback inhibition of bisphosphoglycerate synthase is reduced, and 2,3-bisphosphoglycerate accumulates within red cells. ADP denotes adenosine diphosphate.

hemoglobin releases oxygen in the periphery, its affinity for *S*-nitrosothiol is reduced, and nitric oxide is released into the tissues. The thiol group of *S*-nitrosothiol essentially protects nitric oxide from being scavenged by the binding site on heme. Thus, in addition to carrying oxygen, hemoglobin acts as a carrier of nitric oxide. The enhanced release of nitric oxide from nitrosohemoglobin in hypoxic tissue in turn reduces the regional vascular resistance.²¹ This is another example of an allosteric feature of hemoglobin that enhances oxygen transport by improving the matching of regional oxygen requirements to blood flow.

CLINICAL IMPORTANCE OF HEMOGLOBIN FUNCTION

Optimal P_{50}

The rates of oxygenation of blood in the lungs and deoxygenation of blood in the peripheral-tissue capillaries are determined by the respective mean pressure gradients driving diffusion in the lungs (alveolar oxygen tension - P_{50}) and tissue (P_{50} - mito-

chondrial oxygen tension). For any given combination of maximal cardiac output, alveolar oxygen tension, and diffusing capacities of the lungs and tissue, there is an optimal P_{50} at which the pressure gradients for oxygen loading and unloading are appropriately matched to the transport capacity of each step, as illustrated in Figure 4A²² and by the following equation:

$$\text{oxygen uptake} = (\text{alveolar oxygen tension} - P_{50}) \times \text{diffusing capacity of lung} = (P_{50} - \text{mitochondrial oxygen tension}) \times \text{diffusing capacity of tissue}.$$

If the diffusing capacity of the lungs is low with respect to that of the peripheral tissue, P_{50} must decrease to raise the pressure gradient in the lungs relative to that in the tissues, and vice versa. Thus, a low P_{50} enhances pulmonary oxygen loading, and a high P_{50} enhances peripheral oxygen unloading. There is a constant tradeoff between loading and unloading.

Feedback adjustment is provided mainly by allosteric control of P_{50} through the Bohr effect and temperature, as well as by chemoreceptor control of ventilation. If the P_{50} is too high, loading is impaired and the arterial oxygen saturation drops. Hypoxemia then stimulates ventilation, which increases the alveolar oxygen tension and blood pH and lowers the P_{50} . If the P_{50} becomes too low, unloading is impaired, and the aggravated tissue acidosis raises the P_{50} toward normal.²³ These feedback mechanisms allow oxygen transport to be optimized by appropriate adjustments of the P_{50} .

Exercise at Sea Level

The degree of oxygenation of the blood leaving the lung capillaries at any given values of alveolar and mixed venous oxygen tension is determined by the P_{50} and by the ratio of pulmonary diffusing capacity to cardiac output, which decreases with exercise.^{24,25} When the ratio falls below a critical level, arterial oxygen saturation declines sharply and oxygen delivery is correspondingly curtailed. Raising alveolar oxygen tension by increasing ventilation lowers the critical ratio at which oxygen saturation begins to fall. Raising the P_{50} has the opposite effect.

In the average untrained subject, maximal exercise is not limited by either ventilation or pulmonary diffusion, but rather by a relatively low maximal cardiac output and peripheral oxygen extraction. The alveolar oxygen tension is kept high by ventilatory stimulation, and the ratio of diffusing capacity to cardiac output does not fall below the critical level. Hence, the arterial oxygen saturation is well maintained at peak exercise, even in the presence of a rising P_{50} induced by lactic acidosis and an increased body temperature after prolonged heavy exercise (Fig. 4B).

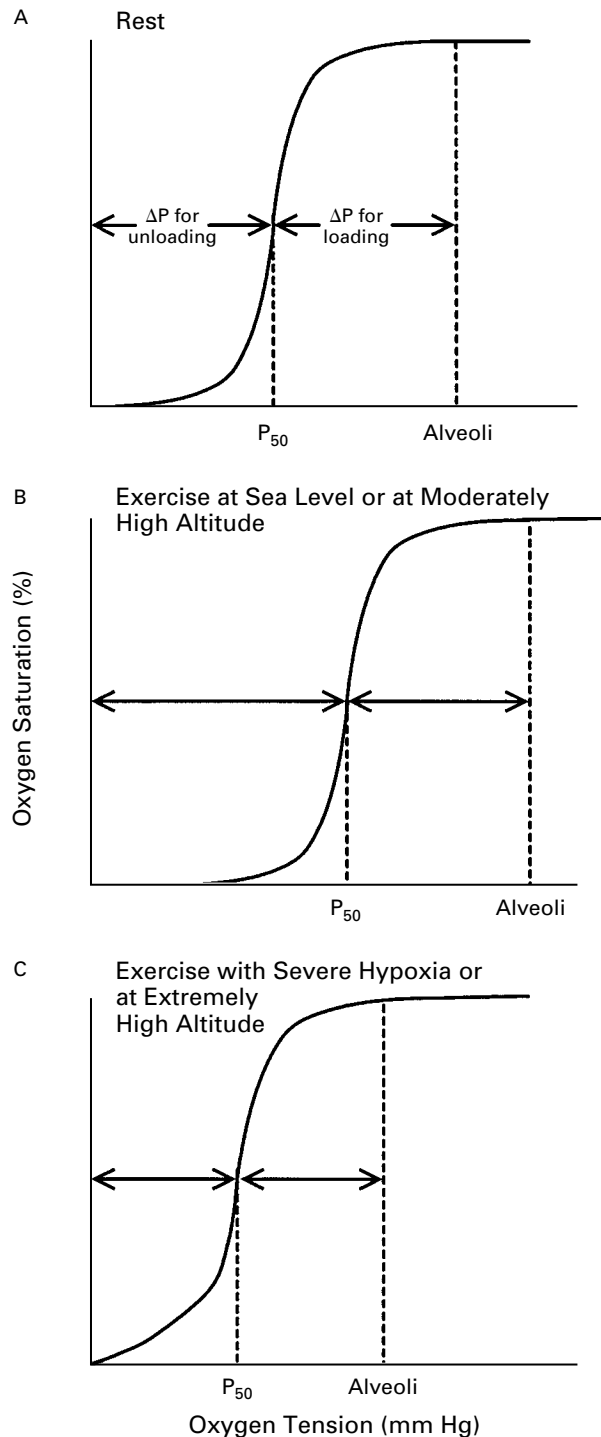
In trained athletes, the maximal cardiac output is

Figure 4. Changes in the P_{50} under Different Conditions.

The difference in oxygen tension (ΔP) between the alveolar air and the pulmonary-capillary blood provides the gradient for oxygen loading in the lungs (Panel A). The difference in oxygen tension between the blood leaving the lungs and the tissue mitochondria provides the gradient for oxygen unloading in the periphery. Optimal oxygen transport is achieved through shifts in the P_{50} that match the gradients for loading and unloading to the respective diffusing capacities of the lungs and tissues. During exercise at sea level or at moderately high altitude, P_{50} is increased to facilitate peripheral oxygen unloading, whereas pulmonary oxygen loading is protected by an increase in alveolar oxygen tension through hyperventilation (Panel B). During exercise under conditions of severe hypoxia or extremely high altitude, the P_{50} is reduced, since the primary limitation is a low alveolar oxygen tension (Panel C). Adapted from Johnson.²²

greatly increased, leading to a much lower ratio of diffusing capacity to cardiac output during peak exercise, so that blood may exit the pulmonary capillaries without being fully oxygenated. Hence, athletes reach the limits of both pulmonary and peripheral oxygen transport. Achieving maximal oxygen uptake may necessitate a drop in arterial oxygen saturation to 85 to 90 percent,²⁶ as illustrated below.

If one knows the diffusing capacities of the lungs and tissues, the alveolar oxygen and carbon dioxide tensions, the cardiac output, the hemoglobin concentration, and the body temperature, it is possible to compute the maximal oxygen extraction and predict the maximal oxygen uptake as a function of P_{50} (Fig. 5, top panel). The P_{50} increases with exercise as a result of tissue acidosis, causing oxygen extraction to increase. The mixed venous oxygen saturation falls (Fig. 5, bottom panel), and the maximal oxygen uptake increases. Concomitantly, the arterial saturation falls, which has the opposite effect (Fig. 5, middle panel). Beyond a critical point, further increases in the P_{50} cause the maximal oxygen uptake to decline. The optimal P_{50} is a point of compromise at which the opposing effects of an increasing P_{50} exactly balance each other, so that the difference in oxygen content between arterial and venous blood and the maximal oxygen uptake are both at their highest possible values. A ventilatory limitation may also be reached during peak exercise, so that the alveolar oxygen tension cannot be increased further to protect pulmonary oxygen loading. Champion athletes must tolerate a marked metabolic acidosis as well as arterial hypoxemia to maximize performance. In animals with high aerobic capacities, the *in vivo* P_{50} during peak exercise corresponds closely to the optimal P_{50} predicted on the basis of hemodynamic and blood gas profiles,²³ indicating the precision with which hemoglobin structure has evolved to meet the functional demands of the organism.



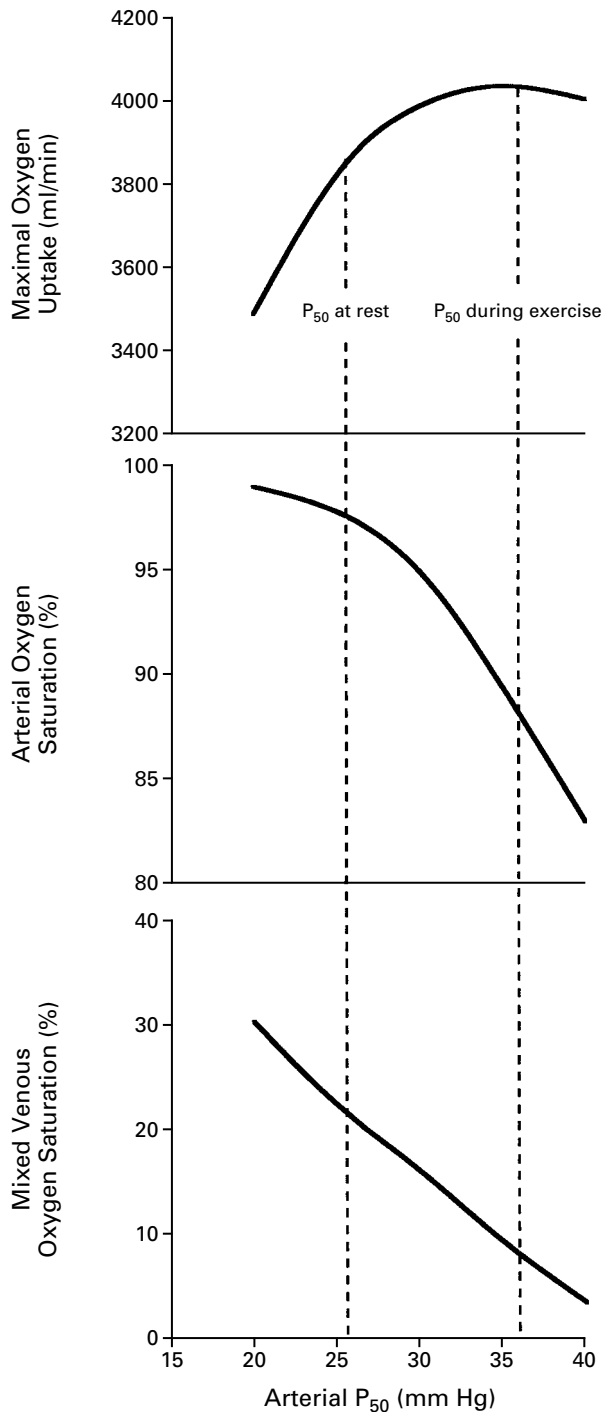


Figure 5. Effects of the P_{50} on Maximal Oxygen Uptake at Sea Level.

During exercise, tissue acidosis and the increase in body temperature cause an increase in the arterial P_{50} , which causes a decline in mixed venous oxygen saturation (bottom panel), allowing greater peripheral oxygen extraction and increasing maximal oxygen uptake (top panel). A rising P_{50} also causes a decline in arterial oxygen saturation (middle panel), which limits oxygen delivery. Optimal oxygen transport is achieved at a P_{50} at which these opposing effects exactly balance. Calculated with data from Wagner et al.²⁷

Adaptation to High Altitude

Since the primary limitation on oxygen transport at high altitude is impaired loading of oxygen onto hemoglobin caused by alveolar hypoxia, the desirable adjustment would be a lower P_{50} (Fig. 4C).²⁸ At moderately high altitude (3100 m), hypoxia induces an increase in the red-cell 2,3-bisphosphoglycerate concentration, which raises the P_{50} to approximately 29 mm Hg at rest.¹⁹ Heavy exercise at 3100 m induces a further increase in the P_{50} to approximately 38 mm Hg, a response similar to that at sea level.²⁹ This seemingly paradoxical increase may be beneficial at rest or during submaximal exercise, as long as oxygen loading can be maintained by raising the alveolar oxygen tension through ventilatory stimulation.³⁰ However, under conditions of severe hypoxia or at extremely high altitude, hyperventilation cannot adequately augment the alveolar oxygen tension, but the associated respiratory alkalosis causes a large decrease in P_{50} .

Elite climbers breathing ambient air at the summit of Mount Everest (elevation, 8800 m; oxygen tension of inspired air, 43 mm Hg) had an alveolar oxygen tension of 35 mm Hg and an arterial oxygen tension of 28 mm Hg.^{31,32} At a normal sea-level P_{50} (26 mm Hg), the expected arterial oxygen saturation (55 percent) is incompatible with consciousness. But the severe hypoxic ventilatory stimulus leads to a profound respiratory alkalosis (arterial pH, >7.7; carbon dioxide tension, 7.5 mm Hg) and a reduction in the in vivo P_{50} to 20 mm Hg,³² raising the actual arterial oxygen saturation to 78 percent at the same arterial oxygen tension. Thus, in severe hypoxia, feedback control of oxyhemoglobin binding allows climbers to achieve adequate saturation for short-term survival without supplemental oxygen.

There is a strong inverse correlation between the P_{50} and the hemoglobin concentration.³³ Subjects with hemoglobin variants that have high affinity for oxygen are usually asymptomatic but often have secondary erythrocytosis, an indication that the high oxygen affinity causes a physiologically important oxygen deficit, even at sea level. On the other hand, high oxygen affinity has a potential advantage for acclimatization to high altitudes. Subjects with hemoglobin Andrew–Minneapolis (P_{50} , 17 mm Hg) maintain normal arterial oxygen saturation at an altitude of 3100 m. As compared with subjects with normal hemoglobin, they have no decrement in maximal oxygen uptake, a smaller increase in heart rate, and no increase in the plasma erythropoietin concentration at high altitude. They have been termed “human llamas.”³⁴ Animals indigenous to high altitudes, such as yaks, llamas, and alpacas, as well as geese that regularly migrate over the Himalayas and the Andes, all have high-affinity hemoglobins (P_{50} , approximately 10 mm Hg lower than that in related

lowland species), achieved through a combination of amino acid substitutions on the globin chain and persistence of fetal hemoglobin.³⁵⁻³⁸

It remains controversial whether highland human populations have undergone similar adaptive changes. Initial reports that indigenous Andean people had hemoglobin with a higher oxygen affinity and a greater Bohr effect were not substantiated by later studies.^{19,39-44} At high altitudes in the Himalayas, indigenous Sherpas have less hypoxia and a lower alveolar-arterial oxygen-tension gradient than acclimatized lowlanders,⁴⁵ which may reflect higher pulmonary diffusing capacity rather than higher hemoglobin affinity. Tibetan highlanders have lower hemoglobin concentrations^{46,47} and smaller red cells than Andeans residing at similar altitudes. High-altitude sickness is virtually unknown among Sherpas but is well documented among Peruvian Indians. Sherpas may adapt better than Andeans to hypoxia because of a longer history of high-altitude residence, but the mechanisms of adaptation are incompletely understood.^{36,48,49}

Sickle Cell Anemia

The substitution of valine for glutamic acid at position 6 of the β chain of hemoglobin leads to sickle cell anemia. Sick cell hemoglobin has a normal affinity for oxygen when in solution. However, whole blood from patients with sickle cell disease has a markedly decreased affinity for oxygen as a result of intracellular polymerization of hemoglobin S and higher levels of 2,3-bisphosphoglycerate.⁵⁰ The Bohr effect is increased in blood from patients with sickle cell disease,⁵¹ and a given drop in tissue pH causes a greater decrease in oxygen affinity. The higher P_{50} facilitates oxygen unloading and explains why the patients can tolerate chronic severe anemia quite well. On the other hand, a higher P_{50} also favors the formation of deoxyhemoglobin, which in turn increases the polymerization of hemoglobin S and may trigger a sickling crisis if the peripheral pH drops.

Effects of Carbon Monoxide

Because the affinity of hemoglobin for carbon monoxide is 200 times its affinity for oxygen, hemoglobin binds alveolar carbon monoxide in preference to oxygen during pulmonary transit, whereas oxygen dissociates more readily than carbon monoxide during tissue transit, leading to an apparent blockade of oxygen diffusion in lung and muscle. Even a minute concentration of carbon monoxide can be lethal if inspired long enough. In addition to reducing the oxygen-carrying capacity of blood, carbon monoxide directly increases the oxygen-binding affinity of hemoglobin and impairs oxygen extraction.⁵² Thus, the blood carboxyhemoglobin concentration consistently underestimates the tissue oxy-

TABLE 1. EFFECTS OF ACID-BASE DISTURBANCES.

TYPE OF DISTURBANCE	HYDROGEN ION (INSTANTANEOUS)	2,3-BISPHOSPHOGLYCERATE (IN 12-24 HR)	P_{50}
Acute acidosis	Increased	Normal	Increased
Chronic acidosis	Increased	Decreased	Normal
Acute alkalosis	Decreased	Normal	Decreased
Chronic alkalosis	Decreased	Increased	Normal
Acute alkalization during chronic acidosis	Normal or decreased	Decreased	Markedly decreased

gen deficit; any given blood carboxyhemoglobin concentration causes greater tissue hypoxia than an equivalent reduction in hemoglobin content caused by anemia.

The effects of carboxyhemoglobin are especially amplified in the placental circulation. Fetal hemoglobin has a high oxygen affinity (P_{50} , 19.4 mm Hg), which facilitates the uptake of oxygen from the hypoxic maternal uterine blood (oxygen tension, 28 mm Hg). Since the normal fetal arterial oxygen saturation is only 75 to 80 percent (on the steep portion of the oxyhemoglobin dissociation curve), the fetus is sensitive to small changes in oxygen tension. Even minor amounts of maternal carboxyhemoglobin can impair fetal oxygen transport. For example, a pregnant woman who smokes a pack of cigarettes a day can easily have a mean blood carboxyhemoglobin concentration of more than 6 percent. This will reduce the maternal P_{50} from 26 to 23 mm Hg and the uterine venous oxygen tension from 38 to 32 mm Hg, leading to a drop in the diffusive gradient driving oxygen across the placenta. Correspondingly, the oxygen tension of fetal umbilical-cord blood will be reduced from 28 to 22 mm Hg, and fetal arterial oxygen saturation from 75 percent to 58 percent.⁵³

Acid-Base Disturbances

In acute acidosis, a higher P_{50} favors oxygen unloading (Table 1). In chronic acidosis, a compensatory reduction in red-cell 2,3-bisphosphoglycerate restores the whole-blood P_{50} to nearly normal, despite a low pH. Acute alkalization of the blood, superimposed on a background of chronic acidosis, may impair both convective and diffusive oxygen transport by two mechanisms. Alkalemia both reduces the cerebral blood flow by causing cerebral vasoconstriction and impairs oxygen release by lowering the P_{50} . Normally, the critical cerebral venous oxygen tension required to maintain an adequate tissue-diffusive gradient is approximately 17 mm Hg.⁵⁴ This threshold is raised in the presence of a higher oxygen affinity

caused by alkalemia. Simultaneously, as the arterial carbon dioxide tension drops and the cerebral blood flow diminishes, the arteriovenous oxygen extraction must be greater in order to maintain cerebral oxygen uptake. These combined effects can lead to cerebral tissue hypoxia, even though blood oxygenation appears adequate.

Aggressive correction of chronic acidosis has particularly detrimental consequences in patients with existing respiratory, cardiac, or cerebrovascular insufficiency, because they cannot adequately augment ventilation, cardiac output, or regional perfusion to compensate for the higher oxygen-binding affinity of hemoglobin.⁵⁴ Thus, in patients with acute exacerbations of chronic respiratory acidosis requiring mechanical ventilation, aggressive normalization of the arterial carbon dioxide tension should be avoided. Similarly, in patients with diabetic ketoacidosis or lactic acidosis, aggressive infusion of bicarbonate to correct the blood pH may greatly impair the release of oxygen in the tissues at a given arterial oxygen saturation. In addition, since the rapid bicarbonate-induced rise in blood pH does not immediately equilibrate across the blood-brain barrier, the central nervous tissue remains acidotic, maintaining a secondary respiratory alkalosis and exaggerating the effects of a rising pH. Symptoms of severe alkalemia, such as tetany, may develop even before the blood bicarbonate concentration returns to normal.

In chronic metabolic alkalosis, a lower P_{50} favors pulmonary oxygen loading but may impair oxygen release in patients with peripheral vascular disease. A compensatory increase in the red-cell 2,3-bisphosphoglycerate concentration occurs within 24 hours to bring P_{50} back to nearly normal. However, in the interim, hypoxic tissue damage may occur if there are rapid fluctuations in volume and acid-base status, such as those associated with vigorous diuresis.

CONCLUSIONS

Hemoglobin actively regulates oxygen transport through the oxyhemoglobin dissociation curve. When the primary limitation to oxygen transport resides in the periphery (heavy exercise, anemia, low-cardiac-output states, or peripheral vascular disease), the P_{50} is increased to enhance oxygen unloading. When the primary limitation resides in the lungs (high-altitude exposure or major lung disease), P_{50} is reduced to enhance oxygen loading. The tradeoff between loading and unloading is regulated by allosteric control of the P_{50} and chemoreceptor control of ventilation, matched to the diffusing capacities of the lungs and tissues. The resultant optimal P_{50} supports the highest rate of oxygen transport in health and disease.

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