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Physiology, Oxygen Transport

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Introduction

Oxygen is essential for ATP generation through oxidative phosphorylation, and therefore must be reliably delivered to all metabolically active cells in the body.[1][2] In the setting of hypoxia, irreversible tissue damage can rapidly occur. Hypoxia can be the result of an impaired oxygen-carrying capacity of the blood (e.g., anemia), impaired unloading of oxygen from hemoglobin in target tissues (e.g., carbon monoxide toxicity) or from a restriction of blood supply. Blood normally becomes saturated with oxygen after passing through the lungs, which have a vast surface area and a thin epithelial layer that allows for the rapid diffusion of gasses between blood and the environment. Oxygenated blood returns to the heart and gets distributed throughout the body via the circulatory system.

The vast majority of oxygen transported in blood is bound to hemoglobin within red blood cells, while a small amount is carried in blood as a direct solute. The unloading of oxygen at target tissues is regulated by a number of factors including oxygen concentration gradient, temperature, pH and concentration of the compound 2,3-Bisphosphoglycerate. The most important indications of effective oxygen transportation are hemoglobin concentration and the oxygen saturation level, often measured clinically using pulse oximetry. Insults to oxygen carrying capacity or oxygen delivery must be rapidly corrected to prevent irreversible damage to tissues.

Organ Systems Involved

The lungs are the respiratory organs responsible for the exchange of gasses between the bloodstream and the atmosphere.[3] Blood entering the lungs typically has a PO2 of 40 mm Hg. Upon passing through the alveolar and pulmonary capillaries, oxygen and carbon dioxide are allowed to equilibrate across the blood-air barrier, resulting in the removal of carbon dioxide from the blood and the absorption of oxygen. Blood leaving the lungs can be expected to have a PO2 of approximately 100 mg Hg.[4] Oxygenated blood will be carried through the cardiovascular system to peripheral tissues, where oxygen will diffuse along its concentration gradient and be delivered to cells. Here, it will act as the terminal electron acceptor in the process of generating adenosine triphosphate (ATP) through oxidative phosphorylation.

Many organs possess compensatory mechanisms for hypoxia, but the mechanism most relevant to the discussion of oxygen transport is the production of the hormone erythropoietin (EPO) by peritubular fibroblasts in the renal cortex.[5] Erythropoietin acts to stimulate the proliferation and differentiation of erythrocytes in red bone marrow--a process known as erythropoiesis. Erythropoiesis results in an increase in the number of erythrocytes (colloquially known as red blood cells), which leads to an increase in total hemoglobin, and ultimately, increased the oxygen-carrying capacity of the blood.

Mechanism

Hemoglobin (Hgb or Hb) is the primary carrier of oxygen in humans. Approximately 98% of total oxygen transported in blood is bound to hemoglobin, while only 2% is dissolved directly in plasma.[6] Hemoglobin is a metalloprotein with four subunits, each composed of an iron-containing heme group attached to a globin polypeptide chain.[7] One molecule of oxygen can bind to the iron atom of a heme group, giving each hemoglobin the ability to transport four molecules of oxygen. Various defects in the synthesis or structure of erythrocytes, hemoglobin, or the globin polypeptide chain can impair the oxygen-carrying capacity of blood, leading to hypoxia.

Regulation of the unloading of oxygen in target tissues is mostly by the concentration of 2,3-bisphosphoglycerate (2,3-BPG) within erythrocytes. 2,3-BPG preferentially binds to and stabilizes the deoxygenated form of hemoglobin, resulting in a lower affinity of hemoglobin for oxygen, and a subsequent increase in availability of free oxygen for consumption by metabolically active tissues. This physiology allows the body to maintain adequate oxygenation of tissues in the setting of decreased PO2 or increased demand for oxygen. These changes often express as shifts in the oxygen dissociation curve, which represents the percentage of hemoglobin saturated with oxygen at varying levels of PO2. Factors that contribute to a right-shift in the oxygen dissociation curve and favor the unloading of oxygen correlate with exertion. These include increased body temperature, decreased pH (due to increased production of CO2), and increased 2,3-BPG. (Figure)

Related Testing

The most important clinical test in assessing the efficacy of oxygen transportation is the concentration of hemoglobin; this is because the vast majority of oxygen in the blood is bound to hemoglobin, while a minimal amount dissolves in plasma water. Henry's law dictates that the amount of dissolved oxygen in plasma water is equal to the PO2 times the solubility constant of oxygen in the blood, which is determined to be 0.003 mL / mmHg O2 / dL blood. Furthermore, the oxygen carrying capacity of hemoglobin is empirically determined to be 1.34 mL O2 / g Hbg.[8] Thus, when the hemoglobin concentration, hemoglobin saturation (SaO2) and PO2 are known, we can calculate the total oxygen concentration of the blood using the following equation:

- $CaO2 = 1.34 * [Hgb] * (SaO2 / 100) + 0.003 * PaO2$.

The saturation of hemoglobin can be determined in a clinical setting through the use of pulse oximetry, which measures differences in absorption of light at specific wavelengths. A notable limitation to this technique is that oxygenated hemoglobin is indistinguishable from hemoglobin that is bound to carbon monoxide. Thus, a person who has suffered exposure to high levels of carbon monoxide may have a normal oxygen saturation as indicated by pulse oximetry, despite lower levels of oxygen bound to hemoglobin.[9]

Pathophysiology

A persistent reduction in oxygen transportation capacity is most often the result of anemia. The definition of anemia is a decrease in the total amount of hemoglobin in the blood (generally less than 13.5 g / dL in males and 12.5 g / dL in females), which results in reduced carrying capacity for oxygen. Anemia can result from disorders leading to the impaired production of hemoglobin (e.g., iron, B12, or folate deficiency), or by the accelerated destruction of hemoglobin, often the result of a defect in hemoglobin structure.

Thalassemias are an important class of inherited disorders resulting in defective production of hemoglobin. An individual with thalassemia has a mutation which impairs production of the globin polypeptide chain of hemoglobin. Thalassemias are classified based upon the number of genes mutated or absent, and whether they encode the alpha globin chain or the beta globin chain. While the presentations and severity of thalassemias vary significantly, they all result in a quantitative defect in hemoglobin production.

Sickle cell anemia ranks as one of the more notable disorders of hemoglobin structure. While the quantity of hemoglobin produced may be normal, a single amino acid substitution of valine for glutamic acid results in a structural defect that promotes the polymerization of deoxygenated hemoglobin. When deoxyhemoglobin polymerizes, it forms fibers that alter the shape of erythrocytes in a process known as sickling.[10] Eventually, repeated stress caused by sickling will damage the membranes of circulating erythrocytes, leading to premature cell death. While sickle cell anemia can remain asymptomatic for a significant time, severe hypoxia may precipitate a sickling crisis, leading to symptoms of generalized pain, fatigue, headache, and jaundice.

Other defects in oxygen transportation may be the result of an environmental toxin, with one example being carbon monoxide poisoning, also known as carboxyhemoglobinemia. The affinity of carbon monoxide for hemoglobin is 210 times that of oxygen.[10] The binding of carbon monoxide to hemoglobin leads to a drastic left shift in the oxygen-hemoglobin dissociation curve, which impairs the unloading ability of oxygen molecules bound to other heme subunits. It is important to note that in the setting of carboxyhemoglobinemia, it is not a reduction in oxygen-carrying capacity that causes pathology, but an impaired delivery of bound oxygen to target tissues.

Questions

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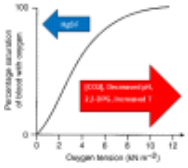

Figure

oxygen dissociation curve. Contributed by Dan Kaufman

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