WCHP Respiratory Physiology 2009-2010
RESPIRATORY GAS TRANSPORT

Clinical rationale and overall goal:

The delivery of oxygen from its site of uptake in the lung to the peripheral tissues, and the simultaneous transport of carbon dioxide in the opposite direction, is essential if normal cellular oxidative metabolism is to occur. The overall goal of this classroom session is to provide the student with an understanding of the basic modes of oxygen and carbon dioxide transport in the blood and the compensations that may occur in these transport systems in the face of disturbances in pulmonary ventilation or pulmonary gas exchange.

Sources of information:

The sources of information that will be sufficient for the individual student to master the specific objectives listed below include the following:

- The required text: Guyton & Hall, *Textbook of Medical Physiology, 11th edition*, Chap. 40;
- Handouts, URLs, reprints or other supplementary materials provided by department faculty;
- Lecture notes

***Nota bene*:** Students are expected to be prepared for class by having read the relevant sections in the text(s) prior to the classroom sessions on individual topics, to take their own notes during classroom sessions, to participate actively in any large-group or break-out group activities, and to try all online quizzes. Students are encouraged to contact the instructor via email (jnorton@une.edu) with any questions. Students are strongly discouraged from using class notes provided by a note service as the sole or even the primary source of information in this course.

Learning objectives:

Following study of appropriate sections in the assigned texts (or similar sections in other texts available to the student and approved by the instructor) and attendance at the lectures on this topic, the student should be able to:

1. Define or otherwise indicate an understanding of the following words or phrases, including units, where appropriate: oxygen dissociation curve; oxyhemoglobin; deoxyhemoglobin; cooperativity; oxygen affinity; P_{50}; hematocrit; 2,3 diphosphoglycerate; myoglobin; carbon monoxide; carboxyhemoglobin; carbon monoxide poisoning; arterio-venous oxygen content difference; dissolved CO_2; bicarbonate ion; carbaminohemoglobin; carbonic anhydrase; chloride shift; CO_2 dissociation curve; arterio-venous carbon dioxide content difference;

2. Recognize the *two modes of transport* of oxygen by blood and indicate which of the two is greater in magnitude and in physiological significance;

3. Recognize the *three modes of transport of carbon dioxide* by blood and rank them in order of magnitude, beginning with the largest;

4. Demonstrate an understanding of each of the following three terms by stating the correct units for each and clearly differentiating among them: *oxygen partial pressure*; *oxygen saturation*; and *oxygen content*;

5. Recognize four factors that affect *hemoglobin-oxygen affinity* and shift the position of the oxygen dissociation curve, either acutely or chronically, and recognize the role of each in maintaining tissue oxygenation;

6. Draw a reasonably accurate representation of the *normal oxygen dissociation curve* (ODC) with appropriate axes, units, and values; locate on this curve typical *arterial* and *venous* points for a healthy human subject at rest; and indicate on the graph using brackets or arrows the *arteriovenous oxygen content difference*;

7. Compare and contrast compare the effects on the oxygen transport system of *carbon monoxide poisoning* and *anemia*;

8. Draw a reasonably accurate representation of the *carbon dioxide dissociation* curve with appropriately labeled axes and values; locate on this curve typical *arterial* and *venous* points; and indicate the *arteriovenous carbon dioxide content difference*;

9. Demonstrate and understanding of the physiological significance of the shapes of the oxygen and carbon dioxide dissociation curves.

10. Given information in a patient case regarding the PO_2 of a blood sample, be able to calculate the total amount of *dissolved oxygen*, as ml O_2 per 100 ml of blood, using the following expression:

$$C_{O_2(\text{dissolved})} = PO_2 \cdot 0.003$$

11. Given information in a patient case regarding the hemoglobin concentration and percent saturation of a blood sample, calculate the *content of oxygen bound to hemoglobin*, as ml O_2 per 100 ml, using the following expression:

$$C_{O_2(\text{bound to hemoglobin})} = [Hb] \cdot 1.34 \cdot \%sat$$

12. Given information in a patient case regarding the hemoglobin concentration, percent saturation, and PO_2 of a blood sample, calculate *total oxygen content*, according to the following expression:

$$C_{O_2(\text{total})} = PO_2 \cdot 0.003 + [Hb] \cdot 1.34 \cdot \%sat$$

13. Given information in a patient case regarding the hemoglobin concentration and oxygen content of a blood sample, calculate the percent saturation;

14. Given a real or simulated description of a patient with chronic arterial hypoxemia, identify all the compensatory changes in the oxygen transport system that would likely be present, using specific data from the case to support your conclusions.

Respiratory Gas Transport

The following discussion is only an attempt to provide the student with a framework for understanding and integrating facts and concepts related to oxygen and carbon dioxide transport, and *the information in this handout is not meant to substitute for attendance in class or completion of the assigned reading in the required textbook*.

Two gas transport problems:

Oxygen: A normal, healthy, 70-kg human subject consumes about 250 ml of oxygen per minute, most of this in the process of oxidative phosphorylation in the mitochondria. Assuming a resting cardiac output of 5 L/min, the job of the blood is to transport a sufficient amount of oxygen from the lungs to the tissues enough oxygen to satisfy tissue demand. The blood must therefore be able to deliver, at rest, 50 ml of oxygen per liter of blood flow and, during exercise or other situations associated with increased tissue oxygen consumption, much more than that.

Oxygen moves from the outside air to the mitochondria by the processes of convection (alveolar ventilation and blood flow) and diffusion (across the respiratory membrane and out of tissue capillaries to cells). Alveolar ventilation and blood flow serve to create, at the sites of diffusional exchange, sufficiently high partial pressure gradients to promote oxygen diffusion in the required amounts. The bulk of the oxygen transported is bound to hemoglobin, with hemoglobin-bound oxygen in equilibrium with dissolved oxygen in the plasma and red blood cell cytoplasm. The delivery of 50 ml of oxygen per liter of blood flow must be accomplished within the change in the partial pressure of oxygen that occurs along the length of the tissue capillary – namely, from the typical arterial PO_2 of 90-95 mm Hg to the typical mixed venous PO_2 of 40 mm Hg.

Carbon dioxide: Transport demands for carbon dioxide can be expressed in a similar fashion. A normal, healthy, 70-kg human subject produces about 200 ml of carbon dioxide each minute, which must be transported from the tissues to the lungs and excreted in the expired air. This requires the transport of 40 ml of CO_2 per liter of blood flow, for a resting cardiac output of 5 L/min. Delivery of carbon dioxide at this rate to the alveolar gas within the lung must occur within the normal partial pressure change for CO_2 that occurs along the length of the pulmonary capillary – namely, from the typical mixed venous PCO_2 of 45-46 mm Hg to the pulmonary end-capillary PCO_2 of 40 mm Hg.

Just how the body can simultaneously transport these two gases, at approximately the rate but in opposite directions, is the topic for this session.

Oxygen transport:

Oxygen is present in blood in two forms: *dissolved oxygen* and *hemoglobin-bound oxygen*. The amount of dissolved oxygen is dependent on the partial pressure of oxygen in the blood and the solubility of oxygen in body fluids. At normal body temperature, the solubility (Bunsen) coefficient for oxygen in body fluids is 0.003 ml O_2 per 100 ml of blood per mm Hg, and the dissolved oxygen content (C_{O_2}) can therefore be calculated as:

$$C_{O_2(\text{dissolved})} = PO_2 \cdot 0.003$$

The student should note that the term C_{O_2} does NOT represent carbon dioxide, CO_2, but the content (C) of oxygen (O_2)! For an arterial PO_2 of 100 mm Hg, the amount of dissolved oxygen would be calculated as $100 \cdot 0.003$, or 0.3 ml O_2/100 ml blood. Because the units are ml/100 ml, oxygen content is sometimes expressed as vol%, so the value for dissolved oxygen calculated in the previous example could also be expressed as 0.3 vol%.

The amount of hemoglobin-bound oxygen is determined by the total amount of hemoglobin and the partial pressure of oxygen. Total oxygen binding capacity can be calculated by multiplying the hemoglobin concentration (in gm Hg/dl blood) by a factor related to the volume of oxygen that can be carried by each gram of hemoglobin, empirically determined as 1.34 ml O_2/gm Hb. For a hemoglobin concentration of 15 gm/dl, for example, the total oxygen binding capacity would be $15 \cdot 1.34 = 20.1$ ml O_2/dl blood, or 20.1 vol%. The actual hemoglobin-bound oxygen content in an arterial or venous blood sample is usually less than this value for maximum oxygen-binding capacity, and is related to the percent of the available oxygen binding sites on hemoglobin that are actually occupied by oxygen molecules, or the *percent saturation*. In arterial blood, oxygen saturation can be as high as 97-98%; in a mixed ven-

ous blood sample from a healthy human subject at rest, the percent saturation is often around 75%. Calculation of the actual hemoglobin-bound oxygen content of a blood sample can therefore be accomplished using the following expression:

$$C_{O_2(\text{bound to hemoglobin})} = [Hb] \cdot 1.34 \cdot \%sat$$

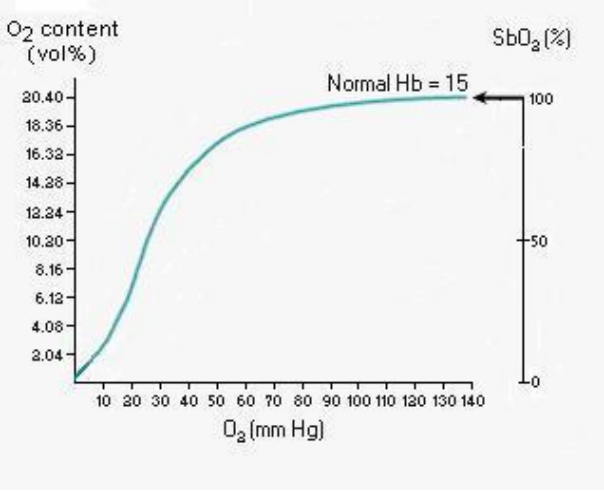
The complete expression for calculating the total oxygen content of blood, given information about PO_2, hemoglobin concentration, and percent saturation, would therefore be the following:

$$C_{O_2(\text{total})} = PO_2 \cdot 0.003 + [Hb] \cdot 1.34 \cdot \%sat$$

It is important to be able to calculate oxygen content from the typical blood gas values provided in an arterial or venous blood sample, because the results provide important information about the amount of oxygen that is actually being transported to the tissues. Measures of blood oxygenation commonly utilized clinically are pulse oximetry, arterial PO_2, and hemoglobin concentration. Pulse oximeters are frequently used to measure percent saturation, based on the differences in the spectral properties of oxyhemoglobin and deoxyhemoglobin, but do not, and *cannot*, provide information about actual oxygen content. A high percent saturation reading on a pulse oximeter may be very misleading in a severely anemic patient, for example, because actual oxygen content would be low. Similarly, because PO_2 reflects only the activity of dissolved oxygen and sheds no light at all on the amount of hemoglobin-bound oxygen, a high value for PO_2 in an arterial blood sample may be misleading. Hemoglobin concentration alone, with any indication of how much oxygen is actually being carried by the hemoglobin, is an insufficient indicator of the adequacy of tissue oxygenation.

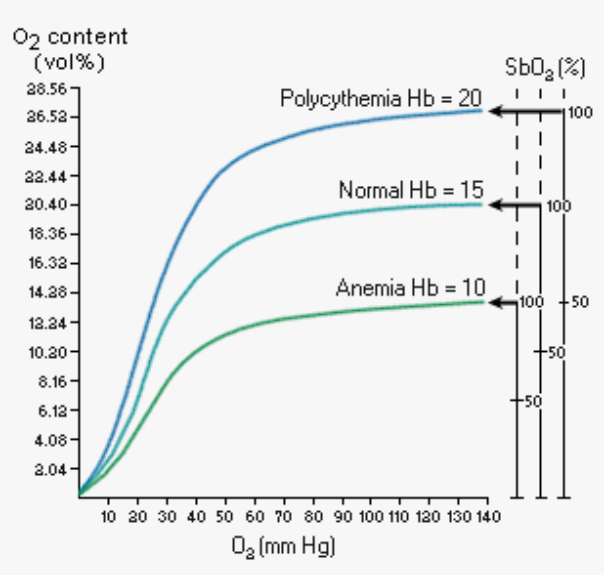
Oxygen dissociation curve:

The relationship between the partial pressure of oxygen in a blood sample and the amount of oxygen bound to hemoglobin is described by the oxygen dissociation curve. The figure below shows an oxygen dissociation curve (ODC) for a hemoglobin concentration of 15 gm/dl. The x-axis is PO_2, in mm Hg; the primary y-axis, on the left of the graph, is oxygen content in vol%. The maximum oxygen binding capacity for this concentration of hemoglobin would be 15·1.34, or 20.1 ml O_2/dl blood (20.1 vol%). If all of the available binding sites for oxygen the heme groups were filled, this would represent 100% saturation, as indicated on the secondary y-axis on the right of the graph. The student should be reminded here that oxygen content is an absolute term, ml of oxygen per 100 ml of blood, whereas percent saturation is a *relative* term that only indicates the percentage of the available oxygen binding sites that are filled.



The relative nature of the term "percent saturation" is illustrated in the figure below, which shows three oxygen dissociation curves corresponding to hemoglobin concentrations of 10, 15, and 20 gm/dl. Again, the x-axis is PO_2, in mm Hg; the primary y-axis, on the left of the graph, is oxygen content in vol%; and the secondary y-axes, on the right of the graph, represent percent saturation. From this figure, it is clear that the actual oxygen content varies in proportion to the hemoglobin concentration, but at the higher values of PO_2, each of the curves approaches 100 %

saturation. For a hemoglobin concentration of 20 gm/dl, maximum oxygen capacity would be 20·1.34, or 26.8 vol%; filling all of this available binding capacity would result in an arterial percent saturation of 100%. For a hemoglobin concentration of 10 gm/dl, maximum oxygen capacity would be 10·1.34, or 13.4 vol%; filling all of this available binding capacity would also result in an arterial percent saturation of 100%. Therefore, a measurement of percent saturation – by an oximeter, for example – reveals nothing about the total amount of oxygen that is being carried by the blood, but is a very convenient and useful way to assess whether the PO_2 is high enough to fill the available binding sites with oxygen.

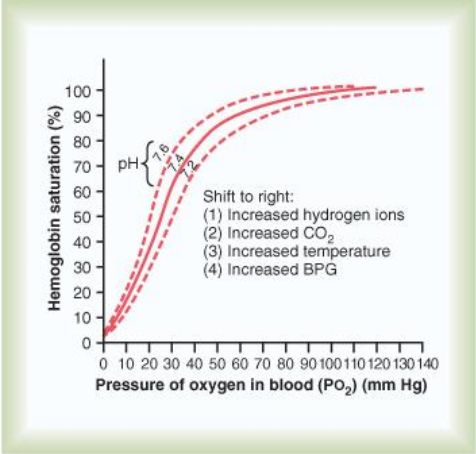


The student should recognize the important fact that increasing hemoglobin concentration will increase the oxygen content of blood at any level of PO_2, and is an important component of the compensatory response to arterial hypoxemia, *whatever the cause*. In hypoxemia, arterial PO_2 and percent saturation are reduced, resulting in a reduction in arterial oxygen content. Increasing the hemoglobin concentration can restore the arterial oxygen content back to normal, *even though the hypoxemia and reduced arterial percent saturation persist!*

The position of the ODC is best described by the P_{50}, or the partial pressure of oxygen at which 50% of the available binding sites for oxygen are filled. Normal P_{50} in a healthy human subject is about 27 mm Hg. An increase in the affinity of hemoglobin for oxygen will be manifested by a decrease in the P_{50} and a shift in the position of the ODC to the left. Conversely, a decrease in hemoglobin-oxygen affinity is manifested as an increase in P_{50} and a shift in the position of the ODC to the right. Left shifts of the ODC that increase oxygen affinity and decrease tissue oxygen delivery are the result of decreases in hydrogen ion concentration (increased pH), PCO_2, temperature, and/or intraerythrocytic 2,3-diphosphoglycerate (2,3-DPG) concentration. Right shifts of the ODC that decrease oxygen affinity and favor tissue oxygen delivery are the results of increases in hydrogen ion concentration (decreased pH), PCO_2, temperature, and 2,3-DPG.

The shifts in oxygen affinity are the result of conformational changes in the hemoglobin tetramer. The binding of oxygen to heme groups increases the oxygen affinity of the remaining heme groups by shifting the hemoglobin tetramer into a "high affinity" or "oxy" configuration. This increase in oxygen affinity facilitates further oxygen loading in the lung. The release of oxygen and the decrease in oxygen binding to hemoglobin in tissue capillaries decreases the affinity of the remaining heme groups by shifting the tetramer into a "low affinity" or "deoxy" configuration, thereby facilitating oxygen delivery in the tissues. "Salt bridges" that form between the globin chains stabilize the "deoxy" conformation of the hemoglobin tetramer. In addition to the effects of oxygen binding to heme groups, the binding of other substances to the globin chains affects oxygen affinity. Increased hydrogen ion concentration (decreased pH), increased PCO_2, and increased 2,3-DPG tend to stabilize the hemoglobin tetramer in the "low affinity" or "deoxy" conformation, decreasing oxygen affinity and facilitating tissue oxygen delivery. In particular, 2,3-DPG stabilizes hemoglobin in the "deoxy" configuration by binding in the cleft between the beta-chains of the hemoglobin tetramer.

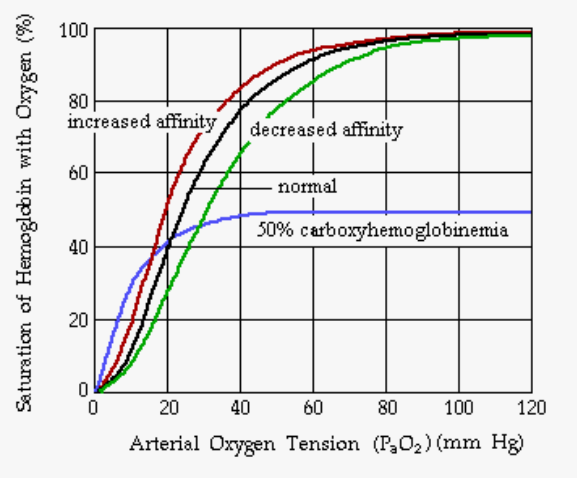
The figure below is a very schematic representation of the shifts in the shape and position of the oxygen dissociation curve (ODC) that can occur in various situations, such as increased hydrogen ion concentration (decreased pH), increased PCO_2, increased temperature, and increased intra-erythrocytic 2,3-DPG (or 2,3-BPG) concentrations.



The effects on oxygen affinity of changes in hydrogen ion concentration, PCO_2, and temperature are immediate, and account for the decrease in oxygen affinity that occurs when blood perfuses a highly metabolically active tissue such as exercising skeletal muscle. The localized change in oxygen affinity that occurs right within the capillaries of such a metabolically active tissue favors oxygen release and tissue oxygen delivery. The oxygen affinity reverts back to normal when the blood leaves the tissue and returns to the lungs. In contrast, the effect of 2,3-DPG on oxygen affinity takes longer to develop, because the erythrocyte needs to synthesize more 2,3-DPG to increase its intracellular concentration and decrease oxygen affinity. The synthesis of 2,3-DPG is stimulated by hypoxemia and the accompanying increase in the concentration of deoxyhemoglobin with erythrocytes. This synthesis of new 2,3-DPG may take a few days, but the ultimate effect is to decrease the oxygen affinity of *all the hemoglobin* throughout the body, *all of the time*, as part of a global compensatory response to hypoxemia, *whatever the cause*. This is very different from the local, transient change in oxygen affinity caused by blood perfusing a highly metabolic tissue or organ and exposed to a warm, acidic environment.

Effects of carbon monoxide on oxygen transport:

Discussing the pathophysiology of carbon monoxide poisoning is useful because it promotes student mastery of the basic mechanisms of oxygen transport and the physiology behind the ODC. The figure below compares shifts in the position of the ODC (the curves labeled "normal", "increased affinity" and "decreased affinity") with a decrease in oxygen carrying capacity caused by binding of carbon monoxide to heme groups in place of oxygen.



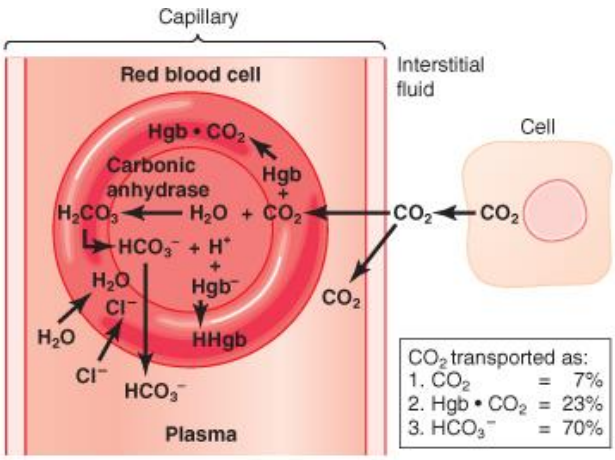
An *arbitrary* level of carbon monoxide poisoning was chosen to represent occupation of 50% of the available oxygen binding sites with carbon monoxide. At this arbitrary level of carbon monoxide poisoning, the oxygen-carrying capacity of the blood would be reduced by 50%, and the highest oxygen saturation that could therefore be produced by high PO_2 levels would be 50%. In addition, close inspection of the oxygen dissociation curves above reveals that the curve representing 50% carboxyhemoglobinemia is shifted to the left. This represents an increased in the affinity of the remaining open heme groups for oxygen, which would impair tissue oxygen delivery in systemic capillaries. Thus, carbon monoxide poisoning is a double-edged sword – it decreases oxygen carrying capacity *and* impairs release of oxygen in the tissues by increasing the oxygen affinity of hemoglobin. In CO poisoning (as in anemia), if alveolar PO_2 is normal and pulmonary gas exchange is not impaired, the arterial PO_2 will be normal.

The student should also be able to compare and contrast the effects on the oxygen transport system of *carbon monoxide poisoning* and *anemia* (shown in a previous figure as the curve labeled "anemia" with a hemoglobin concentration of 10 gm/dl). The table below summarizes the differences between the effects of CO poisoning and anemia on total oxygen-carrying capacity, hemoglobin concentration, arterial oxygen saturation, hemoglobin-oxygen affinity, and arterial PO_2.

	Carbon Monoxide Poisoning	**Anemia**
Oxygen-carrying Capacity	**Decreased** by the occupation of some heme groups by CO, preventing the binding of oxygen	**Decreased** by the reduction in hemoglobin concentration that characterizes anemia
Hemoglobin Concentration	**Normal** in acute carbon monoxide poisoning	**Decreased**
Arterial % Saturation	**Decreased** even at normal arterial PO_2 because some oxygen binding sites are occupied by CO	**Normal** at normal arterial PO_2 because all available heme groups can bind oxygen
Oxygen Affinity	**Increased** because occupation of some heme groups by CO increases the oxygen affinity of the remaining heme groups	**Decreased** because of a compensatory increase in 2,3-DPG
Arterial PO_2	**Normal** because alveolar PO_2 is not significantly diluted by small amounts of CO	**Normal** as long as ventilation and gas exchange are normal

Carbon dioxide transport

The figure below, from the required text, represents the events associated with carbon dioxide uptake by blood in capillaries perfusing metabolically active tissues.



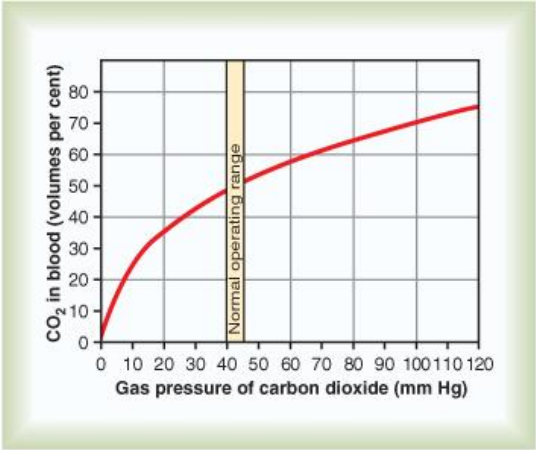
Carbon dioxide diffuses down a partial pressure gradient from cells through the interstitial fluid, into the plasma, and then into erythrocytes, where the enzyme *carbonic anhydrase* facilitates the binding of CO_2 with water to form carbonic acid, which, in turn, quickly dissociates into hydrogen ions and *bicarbonate ions (HCO_3^-)*.

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

As PCO_2 in the blood increases, the excess bicarbonate ion formed inside the red blood cell as the result of the above reaction will move across the erythrocyte membrane into the plasma *via* an anion antiporter in exchange for chloride ions, a phenomenon known as the "chloride shift". The higher the PCO_2, the higher will be the plasma bicarbonate concentration.

The excess hydrogen ion formed inside the erythrocyte by the dissociation of carbonic acid is buffered by hemoglobin. The binding of hydrogen ions to the globin proteins produces the weak acid H^+Hgb^-, and shifts the configuration of the hemoglobin tetramer into the "deoxy", or low-affinity, configuration. This decreases the affinity of hemoglobin for oxygen, shifts the ODC to the right, and facilitates the release of oxygen to the tissues – a phenomenon known as the "Bohr effect". Carbon dioxide also binds to the N-terminal amino acids of the globin chains, to form *carbaminohemoglobin*, which also has the effect of lowering oxygen affinity by favoring the "deoxy" conformation of hemoglobin. In addition to the transport of CO_2 as bicarbonate ions and carbaminohemoglobin, a significant portion of total carbon dioxide transport from the tissues to the lungs occurs as *dissolved CO_2*, due to the relatively high solubility of carbon dioxide in body fluids.

Because of the manner in which carbon dioxide is transported by the blood and because of the relatively high solubility of carbon dioxide compared to oxygen, there is much more carbon dioxide present in the blood than oxygen. The figure below, taken from the required text, shows the CO_2 dissociation curve, relating the partial pressure of carbon dioxide in mm Hg, on the x-axis, to the carbon dioxide content in vol%, on the y-axis.



The student should note that the content of carbon dioxide in the blood, at normal arterial and venous values for PCO_2, is in the range of 50-54 vol%, respectively, compared to oxygen contents of 15-20 vol% at typical normal venous and arterial values of PO_2, respectively. The student should also note that increases or decreases in PCO_2 will produce proportional increases or decreases in the carbon dioxide content of blood, because of the relatively steep slope of the carbon dioxide curve in the range of arterial and venous CO_2 partial pressures. On the other hand, because the oxygen dissociation is relative flat in the normal arterial range, increases and decreases in arterial PO_2 will have little effect on arterial oxygen content, until the arterial PO_2 falls below 60 mm Hg, representing the "shoulder" of the oxygen dissociation curve. This point will be mentioned again in the discussion of the control of ventilation in a later handout and lecture.