# NROSCI/BIOSC 1070 and MSNBIO 2070
# October 18, 2017
# Respiratory 5

## Breathing at High Altitudes

As mentioned earlier in this section, it is very difficult to breathe on top of Mount Everest (altitude of ~ 30,000 feet), because the barometric pressure is so low. As a result, $P_{O2}$ in the air (barometric pressure * 0.21) is also very low. $P_{O2}$ in the alveolus is even lower, as the inspired air is diluted in the residual volume in the lungs. The effects of altitude on gas concentrations in the lung are shown in the following chart:

| **Altitude** (ft) | **Baro. Pres.** (mm Hg) | **$P_{O2}$ in Air** | **$P_{CO2}$ in Alveoli** (mm Hg) | | **$P_{O2}$ in Alveoli** (mm Hg) | | **Arterial Oxygen Saturation (%)** | |
|---|---|---|---|---|---|---|---|---|
| | | | *Unacclimated* | *Acclimated* | *Unacclimated* | *Acclimated* | *Unacclimated* | *Acclimated* |
| 0 | 760 | 159 | 40 | 40 | 104 | 104 | 97 | 97 |
| 10,000 | 523 | 110 | 36 | 23 | 67 | 77 | 90 | 92 |
| 20,000 | 349 | 73 | 24 | 10 | 40 | 53 | 73 | 85 |
| 30,000 | 226 | 47 | 24 | 7 | 18 | 30 | 24 | 38 |
| 40,000 | 141 | 29 | | | | | | |
| 50,000 | 87 | 18 | | | | | | |

### Breathe Pure Oxygen

| **Altitude** (ft) | **Baro. Pres.** (mm Hg) | **$P_{O2}$ in Alveoli** (mm Hg) | **Arterial Oxygen Saturation (%)** |
|---|---|---|---|
| 0 | 760 | 673 | 100 |
| 10,000 | 523 | 436 | 100 |
| 20,000 | 349 | 262 | 100 |
| 30,000 | 226 | 139 | 99 |
| 40,000 | 141 | 58 | 84 |
| 50,000 | 87 | 16 | 15 |

Note that chronic exposure to high altitude (acclimatization) improves blood oxygenation in this environment. We will discuss the process of acclimatization shortly.

At high altitudes (e.g., the cockpit of an unpressurized airplane), it would be impossible to survive while breathing air. However, breathing pure oxygen improves the situation greatly, as shown in the table to the left. Nonetheless, at very high altitudes the barometric pressure is so low that one cannot survive even when breathing pure oxygen.

## Acclimatization to Low $P_{O2}$

A person remaining at high altitudes for a long period of time becomes more acclimated to low $P_{O2}$. The mechanisms involved are:

1) A great increase in pulmonary ventilation
2) Increased number of red blood cells
3) Changes in the oxygen-hemoglobin dissociation curve
4) Increased vascularity of the tissues
5) Increased efficiency of cellular aerobic metabolism

Each of these mechanisms is discussed in detail below.

### *1) A great increase in pulmonary ventilation*

Immediately on exposure to low $P_{O2}$, the hypoxic situation induces an increase in pulmonary ventilation. However, acutely this increase in ventilation is not large, as the decrease in blood $P_{O2}$ (due to altitude) is accompanied by a decrease in $P_{CO2}$ (as hyperventilation acts to lower $P_{CO2}$ in the alveoli). Furthermore, pH of the blood increases (becomes less acidic) when $P_{CO2}$ of the plasma drops. Because chemoreceptor activity is determined by $P_{O2}$, $P_{CO2}$, and pH, the effects of lowered $P_{O2}$ on ventilation are offset by the lowered $P_{CO2}$, and increased pH. However, over the next few days the kidney acts to normalize pH of the blood. Thus, within a few days after moving to a higher altitude, ventilation can increase markedly, up to 4 times that which normally occurs at sea level.

### *2) Increased number of red blood cells*

As we have discussed in previous lectures, hypoxia causes the kidney to release **erythropoietin**, which induces pluripotent hematopoietic stem cells in the bone marrow to differentiate into erythrocytes. Thus, the hematocrit increases. Blood volume also increases over time, and often people living at high altitude have a 50% increase in circulating hemoglobin, but a hematocrit of 60.

### *3) Changes in the oxygen-hemoglobin dissociation curve*

Effects of altitude on the oxygen-hemoglobin dissociation curve are complex. At the onset of hypoxia, the curve tends to shift to the ***left***, as a result of alkalosis induced by hyperventilation (and reduction of plasma $P_{CO2}$ ). Over time, production of **2,3-DPG** by erythrocytes tends to pull the curve back to the right, so that in a fully-acclimated person hemoglobin has approximately the same affinity for oxygen as that of a person living at sea level.

However, these adaptations make good sense. During acute hypoxia, the left-shift of the oxygen-hemoglobin dissociation curve helps to oxygenate the blood in the lungs. This is important, as the alkalosis that is present suppresses an increase in ventilation, so that $P_{O2}$ in the alveoli is low. Over time, as ventilation increases (as the kidney acts to stabilize blood pH) and the amount of hemoglobin in the blood also increases, it is practical to shift the curve back to the right.

### *4) Increased vascularity of the tissues*

As hypoxia continues over time, the vascularity of the tissues, including the number of capillaries, increases. This adaptation vastly increases the ability to oxygenate the tissues. The increased capillarity also occurs in the lungs, and thus the surface area for gas exchange between the alveoli and blood increases. The result of the latter adaptation is increased diffusing capacity for $O_2$ through the pulmonary membrane.

### *5) Increased efficiency of cellular metabolism*

It has been noted that animals native to high altitudes have more mitochondria and some cellular oxidative enzymes than animals living at sea level. It is assumed that such adaptations also occur in humans.

### Chronic Mountain Sickness

Occasionally, exposure to high altitude over a long time has devastating effects on an individual. Polycythemia becomes so severe that blood flow to tissues becomes restricted, and thus the tissues are deprived of oxygen. In some cases, there is also a decrease in lung circulation, as low $P_{O2}$ tends to cause vasoconstriction in the lungs. As this occurs, the right side of the heart becomes enlarged. Eventually, congestive heart failure ensues and the patient dies. However, this disease has a simple treatment: moving the patient to a lower altitude.

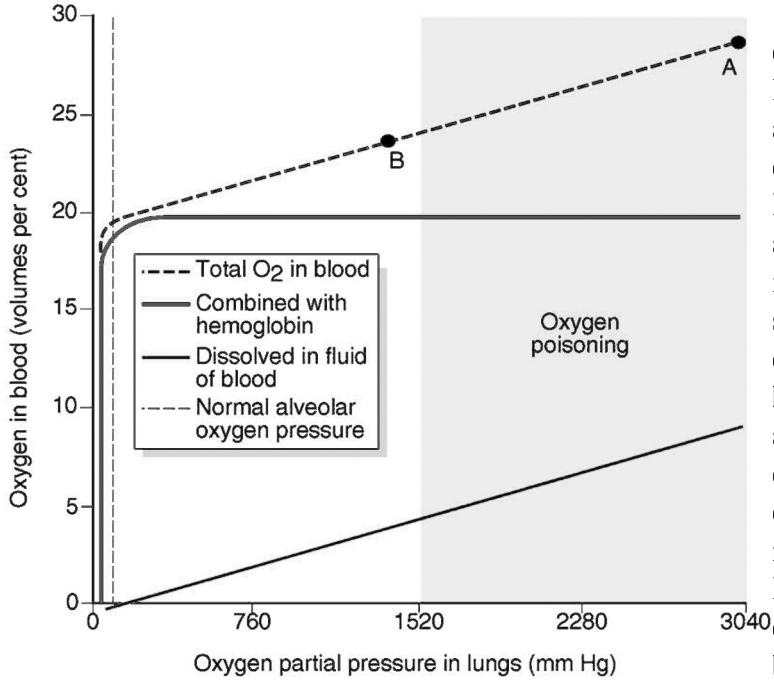
## Effects of Diving on Pulmonary Physiology

When an individual dives, the pressure around him increases tremendously. A column of water 33 feet deep exerts an atmosphere of pressure, so a dive of only 33 feet exerts a pressure outside the body of 2 atmospheres (that of the air [1 atmosphere] plus that added by the water [1 atmosphere]). At 66 feet, 3 atmospheres of pressure are applied to the body, etc. A fairly modest dive of 100 feet applies 4 atmospheres of pressure to the body. To keep the lungs from collapsing, the pressure of the air supplied to the diver must be equal to the pressure of the water around him. As a result, the pressure of gas in the alveoli becomes very high.

Another important effect of depth is the compression of gases to smaller volumes. Thus, a liter of oxygen at sea level only occupies 0.5 liters at 33 feet.

### Effect of High Partial Pressures of Gases on the Body

A diver typically breathes compressed air (containing nitrogen, oxygen, and carbon dioxide). Nitrogen is by far the most prevalent gas, and occupies 80% of the volume of the mixture. Because nitrogen partial pressure in the alveoli and blood becomes so high during diving,nitrogen can become toxic. Nitrogen dissolves in the membranes of neurons, and alters ionic conductances. In effect, it acts as an anesthetic that reduces neuronal excitability. The effect of nitrogen on the nervous system begins at depths of 120 feet; at this depth, the diver becomes very jovial and carefree. At depths greater than 200 feet, the diver feels very sleepy. At depths greater than 250 feet, the diver often becomes comatose. Nitrogen toxicity at depths has characteristics similar to alcohol intoxication, and is sometimes called “raptures of the depths.”

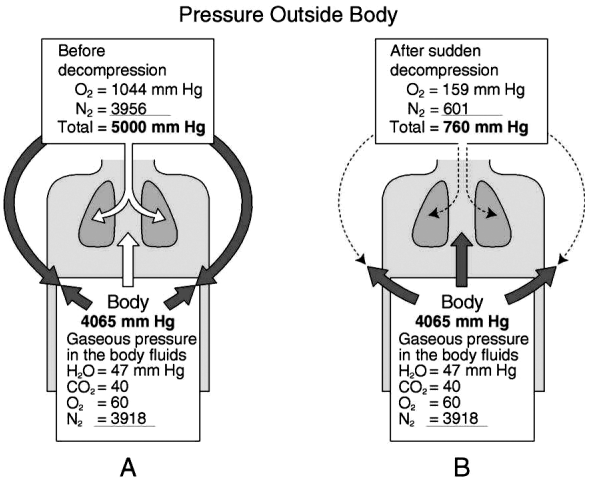



When alveolar $P_{O2}$ increases at great depths, plasma $P_{O2}$ also increases. At sea level, the oxygen dissolved in plasma only accounts for a small fraction of the total oxygen carried by the blood. However, as $P_{O2}$ increases to thousands of mm Hg, an appreciable amount of oxygen is dissolved in the plasma, as hemoglobin becomes saturated and cannot "buffer" this amount of oxygen. Because plasma $P_{O2}$ is so high, the tissues are exposed to very high amounts of oxygen. At high pressures, oxygen begins to form free radicals that oxidize polyunsaturated fatty acids in the membranes as well as some enzymes. Because neural tissue has a high lipid content, it is very susceptible to damage by the free radicals. Seizures often occur after exposure to great depths because of this damage. The lining of the alveoli and bronchi can also become damaged because of high $PO_2$ in the airways.

Carbon dioxide toxicity is not typically a problem for divers. Most alveolar $P_{CO2}$ is that which results from cellular metabolism (i.e., is produced by the body). Thus, even at great depths the $P_{CO2}$ in the plasma and alveoli does not change appreciably.

## Effects of Rapid Decompression

Decompression sickness after returning to the surface is due to the fact that considerable nitrogen becomes dissolved in the body when at great depths. At sea level, about 1 liter of nitrogen is dissolved in the body, largely in fat tissue (as nitrogen is very soluble in lipids). After exposure to high partial pressures of nitrogen during diving, much more nitrogen is dissolved in the body. For example, at 33 feet of depth, 2 liters of nitrogen become dissolved in the tissues, and 4 liters are dissolved at 100 feet of depth. Because nitrogen does not dissolve well in water, it takes considerable time for nitrogen to reach equilibrium in the body (i.e., to be transported to and dissolved in the fat, where it is stored).




Thus, if a diver has been submerged long enough for considerable nitrogen to be dissolved in his tissues, and then he suddenly returns to the surface, the nitrogen begins to precipitate out of the tissues, forming bubbles that can produce damage. These bubbles can block blood vessels, resulting in tissue ischemia. Often, this ischemia affects muscles, resulting in the "bends." However, strokes, heart attacks, and other serious complications can accompany rapid decompression.

To avoid "the bends," a diver must decompress slowly, allowing the nitrogen to precipitate out of the tissue slowly. If a diver works at a depth of 200 feet for 1 hour, it takes 3 hours to safely decompress from this exposure.

Extremely deep dives are possible if the proper precautions are taken. Often divers will acclimate to the new environment by living in compression chambers. While underwater, the diver usually breathes a mixture of 1-2% oxygen and 98-99% helium. Helium is an inert gas that does not have the solubility or toxic effects that nitrogen has. The oxygen concentration is reduced to a low level so that oxygen toxicity will not occur.

## Acid-Base Balance

The normal range of pH in the plasma is very narrow: 7.38-7.42. Intracellular proteins such as enzymes and membrane channels are particularly sensitive to pH because a change in pH alters their three-dimensional structure. If blood pH becomes too low, **acidosis** occurs. If blood pH becomes too high, **alkalosis** occurs.

The biggest source of acid on a daily basis is the production of $CO_2$ during aerobic respiration. As noted previously, $CO_2$ combines with water to form carbonic acid.

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

This reaction occurs spontaneously, but is especially efficient in cells that contain the enzyme **carbonic anhydrase**, which catalyzes the production of carbonic acid.

A number of buffer systems exist in the body to maintain stable pH. Intracellular buffers include phosphate ions and hemoglobin. The major extracellular buffer is bicarbonate ion, which is released from red blood cells as part of the **chloride shift**. Thus, the predominant "waste product" of aerobic metabolism is converted into the body's major buffer.

If a person hypoventilates, then $P_{CO2}$ increases, resulting in an increase in $H^+$ and $HCO_3^-$. Because acid is increasing in the plasma, pH drops. This condition is called **respiratory acidosis.**

$$\uparrow CO_2 + H_2O \leftrightarrows H_2CO_3 \leftrightarrows \uparrow H^+ + \uparrow HCO_3^-$$

If a person hyperventilates, then $P_{CO2}$ decreases, resulting in a decrease in $H^+$ and $HCO_3^-$. Because acid is decreasing in the plasma, pH increases. This condition is called **respiratory alkalosis.**

$$\downarrow CO_2 + H_2O \leftrightarrows H_2CO_3 \leftrightarrows \downarrow H^+ + \downarrow HCO_3^-$$

Respiration is not the only process that can change blood pH. An increase in anaerobic activity in muscles results in the production of lactic acid, which can acidify the blood. The GI tract can also release $H^+$ into the blood as a by-product of synthesis of secretions. When such metabolic processes lower blood pH, **metabolic acidosis** is present. **Metabolic alkalosis** occurs when metabolic processes reduce $H^+$ in the blood. Overproduction of some GI secretions can produce this condition.

The body has three lines of defense to prevent alkalosis and acidosis. The first line of defense is formed by the buffer systems. The second line of defense is ventilation. Metabolic acidosis is counteracted by hyperventilation, and metabolic alkalosis is counteracted by hypoventilation. The changes in ventilation when blood pH changes are triggered by the chemoreceptors, which increase their activity when pH drops. The third line of defense against acidosis and alkalosis is the kidney, which can excrete either $HCO_3^-$ or $H^+$. The role of the kidney in maintenance of stable pH was

discussed in the renal section of the course.

The following table shows how acidosis and alkalosis affect $H^+$, pH, and $HCO_3^-$ in the body:

| Disturbance | $P_{CO2}$ | $H^+$ | pH | $HCO_3^-$ |
|---|---|---|---|---|
| ***Acidosis— Respiratory*** | ↑ | ↑ | ↓ | ↑ |
| ***Acidosis— Metabolic*** | No change or ↓ | ↑ | ↓ | ↓ |
| ***Alkalosis— Respiratory*** | ↓ | ↓ | ↑ | ↓ |
| ***Alkalosis— Metabolic*** | No change or ↑ | ↓ | ↑ | ↑ |

The **Henderson-Hasselbalch Equation** quantitatively describes the relationship between $P_{CO2}$, pH, and $HCO_3^-$. In human blood, the equation can be stated as follows:

$$\mathbf{pH=6.1+Log([HCO_3^-]/0.03*P_{CO2})}$$

In this equation, $[HCO_3^-]$ = bicarbonate concentration in mmol/L

The constant 0.03 reflects the solubility of $CO_2$ in water (in mmol/L per mm Hg)

6.1 is the $pK_a$ of carbonic acid. Recall that $pK_a$ reflects the pH at which the ratio [A]/[HA], or in this case $[HCO_3^-]/[H_2CO_3]$, equals 1.

The Henderson-Hasselbalch Equation is based on the equilibrium between carbonic acid and its dissociation products:

$$\mathbf{H_2CO_3 \leftrightarrows H^+ + HCO_3^-}$$

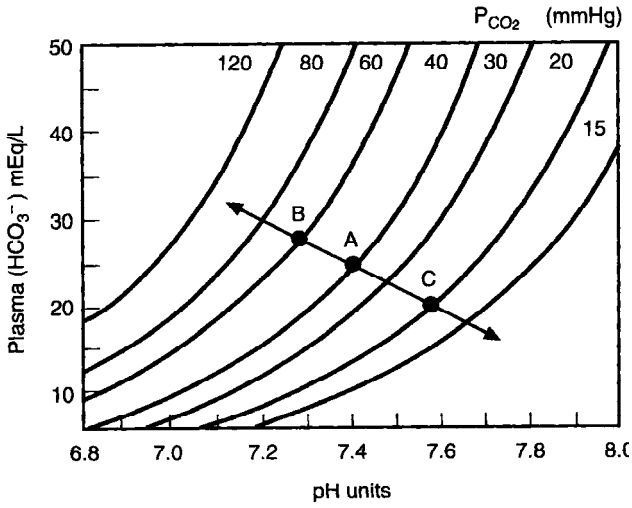
The dissociation constant for a weak acid ($K_a$) like carbonic acid is calculated as follows:

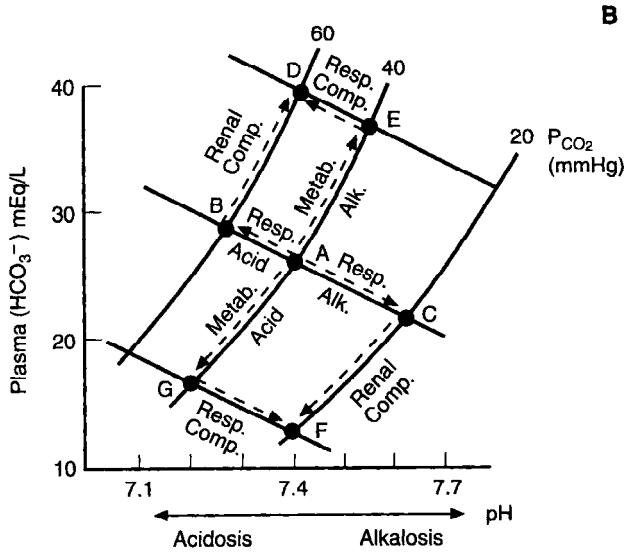
$$\mathbf{K_a = [H^+]*([HCO_3^-]/[H_2CO_3])}$$

Knowing that $pH= -\log_{10}[H^+]$ and $pK_a= -\log_{10}(K_a)$, the Henderson-Hasselbalch Equation can be derived algebraically. The term $(0.03*P_{CO2})$ can replace $[H_2CO_3]$, as total carbonic acid is proportional to dissolved $CO_2$ in the blood.

The normal value for $[HCO_3^-]$ is 24 mmol/L, and normal $P_{CO2}$ is 40, thus pH of the blood is :

$$\mathbf{6.1+Log([HCO_3^-]/0.03*P_{CO2})=6.1+Log(24/[0.03*40])=7.4}$$




The relationship between pH, $[HCO_3^-]$, and $P_{CO2}$ can be illustrated through the bicarbonate-pH diagram. Note that increasing carbonic acid production (moving from point A to point B) both increases the amount of bicarbonate and lowers pH. Lowering carbonic acid production (moving from point A to point C) has the opposite effect. This type of graph also illustrates the effects of metabolic acidosis and alkalosis on bicarbonate levels and pH.