Respiratory System Physiology

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The underlined headings correspond to the eight Respiratory System videos.

1. Anatomy and Mechanics

Introduction

The respiratory system carries out several homeostatic functions, including:

1. **gas exchange** between the atmosphere and the blood to provide an adequate supply of oxygen to tissues and to remove carbon dioxide (CO_2) generated in oxidative metabolism.

$$O_2 + Food = CO_2 + H_2O + ATP$$

2. **regulation of body pH** by either retaining or eliminating CO_2
3. **conversion of angiotensin I to angiotensin II** which acts to control blood pressure
4. **protection from inhaled particles**.

In the respiratory system, air flow occurs by **bulk flow** from regions of high pressure to lower pressure with the pressure differences generated by a muscular pump. Resistance to air flow is influenced primarily by the radius of the tube ($1/r^4$) through which air is flowing.

$$F = (P_1 - P_2)/R$$

The movement of fresh air into the lung (inspired) or out of the lung (exhaled) is called **ventilation**. Both the rate and size of the breath (**tidal volume**) can change in response to needs of the body.

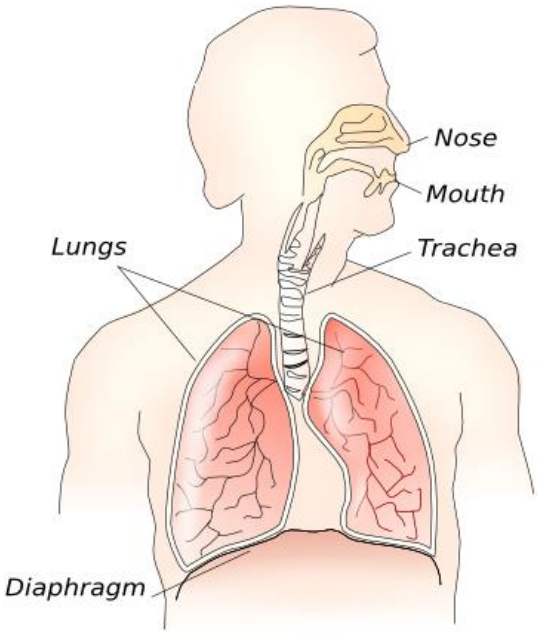

Figure 1 Anatomy of the respiratory system. Image by OCAL, http://www.clker.com/clipart-12109.html, public domain

Anatomy

The respiratory system consists of structures involved in moving air into and out of the lungs (bulk flow) and in gas exchange (diffusion).

LUNGS AND CHEST WALL act as a unit. Each lung is surrounded by a membranous sac (pleura) filled with a thin film of fluid (Fig. 1). This intrapleural fluid serves as a lubricant so the lungs can move freely within the chest wall and functionally connects the lungs to the chest wall such that expansion of the chest expands the lungs.

CONDUCTING ZONE leads from the external environment to the gas exchange surfaces of the lungs (Fig. 1). This zone includes a series of tubes (nasal cavity, pharynx, trachea, bronchus, and bronchioles) with small radii and small surface areas. Their total volume is about **150 ml**. Since no gas exchange occurs in the conducting zone, it is often called the **anatomical dead space**.

RESPIRATORY ZONE is the region of the lung where gas exchange occurs (Fig. 2). The respiratory zone is much larger than the conducting zone and has a volume of about **3 L**. It consists of respiratory bronchioles, alveolar ducts and alveoli. The alveoli are small sac-like structures with very thin walls wrapped by capillaries (Fig. 2). The 300 million alveoli provide a surface area of about 70 m^2. Here oxygen (O_2) diffuses from the air space to the blood and carbon dioxide (CO_2) diffuses from the blood to the air space. The distance that gas has to diffuse is very short, about 0.2 microns, making the alveolus-capillary unit ideally suited for gas exchange.

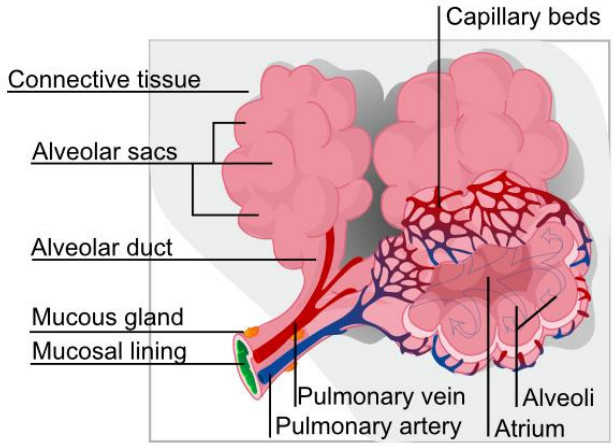

Figure 2. Respiratory zone of the lung. Image by Mohamed Ibrahim , http://www.clker.com/clipart-49452.html, public domain

TYPE I CELLS are thin epithelial cells that line about 90% of the surface area of the alveoli. Gases diffuse across the type I cells to and from the blood (Fig. 2).

TYPE II CELLS are interspersed among the type I cells. Type II cells synthesize, secrete, and metabolize alveolar surfactant. Surfactant is a lipid-rich substance that lines the alveoli and helps keep lungs from collapsing.

ALVEOLAR MACROPHAGES are the third type of cell found in alveoli. Macrophages engulf inspired particles such as bacteria. These cells are mobile and are attracted to areas of either infection or trauma.

Pulmonary Function

BREATHING is the process of **inspiration** (air flows into the lung) and **exhalation** (air flows out of the lung).

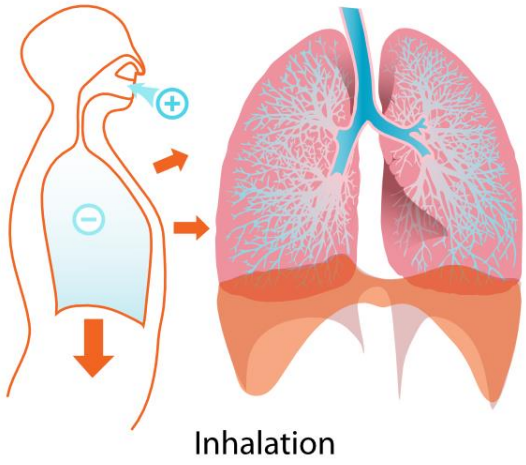

Figure 3. Expansion and contraction of the alveolar space alters the pressure of air within. Image by Mohamed Ibrahim, http://www.clker.com/clipart-49504.html, public domain

Inspiration begins when the diaphragm and the intercostal muscles of the chest wall contract in response to neural impulses from the brain stem (Fig. 3). Contraction of the diaphragm causes it to descend and contraction of the intercostal muscles raises the ribs; the chest cavity expands. Because the lungs are functionally connected to the chest wall by the pleural sac, the lungs also expand (Fig. 3). This increase in lung volume reduces the air pressure in the alveolar ducts and alveoli. When the pressure in the alveoli (P_A) becomes less than the pressure at the mouth, which is ordinarily atmospheric pressure (P_{atm}), air flows in until $P_A = P_{atm}$ (Fig. 3).

Exhalation occurs when the muscles of inspiration relax. The lung returns ***passively*** to its pre-inspiratory volume due to its elastic properties. This reduction in volume raises the pressure in the lung causing air to flow out.

VENTILATION CYCLE is one inspiration and exhalation. Ventilation rate (*f)* is in the range of 10-18 breaths per min. Both the rate and depth can be changed by output from the respiratory centers in the brain stem (medulla oblongata). During heavy exercise air flow can increase 20-fold and blood flow 3-fold. To expel such increased volumes, active exhalation is required in which abdominal muscles and internal intercostals muscles contract. These actions actively decrease the size of the thorax (chest cavity).

2. Lung volumes and compliance

LUNG VOLUMES are determined by the interaction of the lung and chest wall. The lungs are elastic like a rubber band. They expand during inspiration and recoil passively during exhalation. Functional residual capacity (FRC) is the resting volume of the lung and chest wall. It occurs when the elastic recoil of the lung (pulling inward) balances the pressure of the chest wall to expand (pulling outward). When chest wall muscles are weak, FRC decreases.

Lung volumes play a major role in gas exchange and in the work of breathing. They are measured under dynamic and static conditions. Dynamic volumes refer to measurements made when volumes are changing, i.e., during gas flow. Static volumes can be measured between two points where there is no flow, for example before and after inspiration.

There are four standard lung volumes (Fig. 4). There are also four standard lung capacities, which consist of a combination of two or more volumes. A spirometer is used to measure lung volumes directly. All volumes except the residual volume (amount of air remaining in the lung at all times) can be measured with a spirometer.

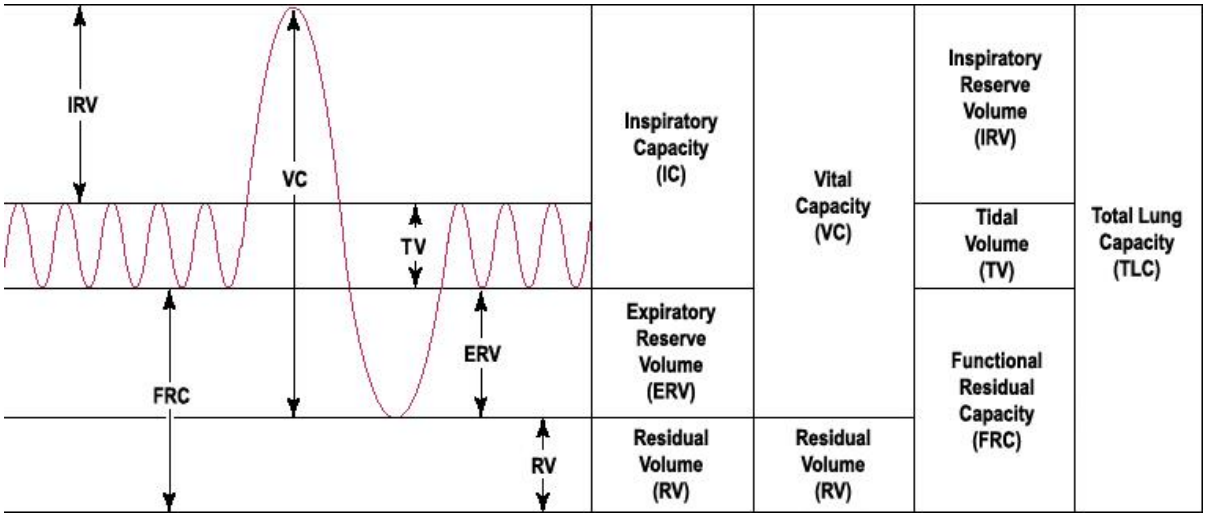

Figure 4. Lung volumes and capacities. image by Vihsadas (modified), http://commons.wikimedia.org/wiki/File:LungVolume.jpg, public domain

Residual volume (RV): Amount of air in the lungs at the end of maximal exhalation (~ 1.5 L young men).

Tidal volume (TV): Volume of air inhaled or exhaled with each breath (in adult males ~ 0.5L; in females usually about 20- 25% less).

Inspiratory reserve volume (IRV): Volume of air that can be inspired after a normal inspiration (~ 3.0 L in males).

Expiratory reserve volume (ERV): Maximal volume of air that can be expired (exhaled) from resting expiratory level (~1.0 L in males).

Inspiratory capacity (IC=TV+IRV): Maximal volume of air that can be inspired from resting expiratory level (~3.5 L in males).

Functional residual capacity: (FRC=RV+ERV): Volume of air in lungs at end of a normal exhalation. (~2.5 L in males) (see Fig. 4).

Vital capacity (VC=ERV+TV+IRV): Volume of air that can be exhaled after maximal inspiration (~ 4.5 L)

Total lung capacity (TLC=RV+ERV+TV+IRV): Volume in lungs at end of maximal inspiration (~6 L).

Changes in lung volumes are some of the earliest indicators of lung disease. One of the most informative is the ratio of RV and TLC. Normally RV/TLC ratio is less than 0.25, that is the air trapped in the lung is ~25% of the total lung volume. In obstructive lung diseases the amount of trapped air (RV) increases, hence RV/TLC increases. In restrictive lung disease in which the lung can not fill normally, RV/TLC also increases but in this case, total lung volume (TLC) is reduced disproportionate to residual volume.

Elastic Recoil and Compliance

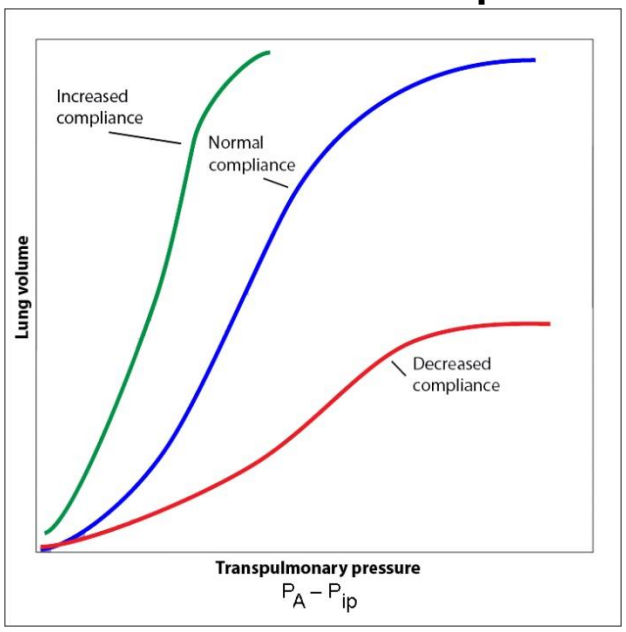

Figure 5. Pressure-volume relationship during inflation of isolated lungs. In the restrictive lung disease, fibrosis, the lung shows decreased compliance and reduced volume (vital capacity). The emphysema lung shows increased compliance and increased volume (vital capacity). Image by Rick Melges, Duke University.

LUNG COMPLIANCE is defined as the stretchability of the lung for any 1-cm change in pressure across the lung.

$$C_L = \triangle V_L / (P_A - P_{ip})$$

The greater the compliance, the easier it is to expand the lungs at any given change in trans-pulmonary pressure. **Compliance is the *inverse of elastic recoil or stiffness*.**

The most common way to obtain a **compliance curve** is to have an individual inspire to total lung capacity and then exhale slowly in small increments. When airflow is temporarily stopped, volume and transpulmonary pressure are recorded. A pressure-volume curve is constructed (Fig. 5). The **slope of the pressure - volume curve at any given point is lung compliance at that point**.

Note that the pressure-volume curve is not linear (Fig. 5). At high lung volumes, the lungs are almost maximally stretched and a large change in pressure produces only a small change in

volume. Therefore, compliance is usually measured in the mid-range of the pressure - volume curve during tidal volume breathing. A normal value for lung compliance at this point is 0.2 liter/cm H_2O.

Lung compliance is determined in part by the elastic tissue of the lung. A lung with high compliance is easy to stretch. The disease **emphysema** destroys this elastic tissue and thus increases lung compliance. A lung with low compliance is stiff and hard to stretch and so is hard to fill with air. This is seen in the disease **fibrosis** (Fig. 5).

Compliance of the lung is determined also by the surface tension generated at the air-water interfaces within the alveoli. The alveoli are air filled sacs lined with water. The attractive force between the water molecules (known as surface tension) resists stretching. The surface tension of pure water is so great that were the alveoli lined by water alone, lung expansion would require exhausting muscular effort and the lungs would tend to collapse. The detergent-like substance, **surfactant**, markedly reduces this surface tension and thereby increases lung compliance.

Lung surfactant is synthesized by the **alveolar type II cell** and secreted into the alveolar space by stretching the type II cells during breathing. The major component in surfactant is a phospholipid which is inserted perpendicularly into the gas-liquid interface so that its non-polar, hydrophobic fatty acids are pointed toward the gas and its polar end is in the liquid. The phospholipids form a monolayer that generates a film pressure opposing the surface tension. When this film is compressed (as the volume of the lungs is reduced) the film pressure rises and surface tension falls even further. This property stabilizes the lungs.

The lungs of many premature babies are unable to produce adequate amounts of functional surfactant. Approximately 50% of babies born before the 31st week of gestation will suffer from *Respiratory Distress Syndrome*. Because of the lack of surfactant, the surface tension in their lungs is high, which increases the tendency of the lungs to collapse. *Do these lungs have high or low compliance?*

Surfactant stabilizes the alveoli. The surface tension of the alveoli tends to pull inward creating a pressure. The relationship between surface tension and pressure is shown in Figure 6 and is defined by the law of Laplace.

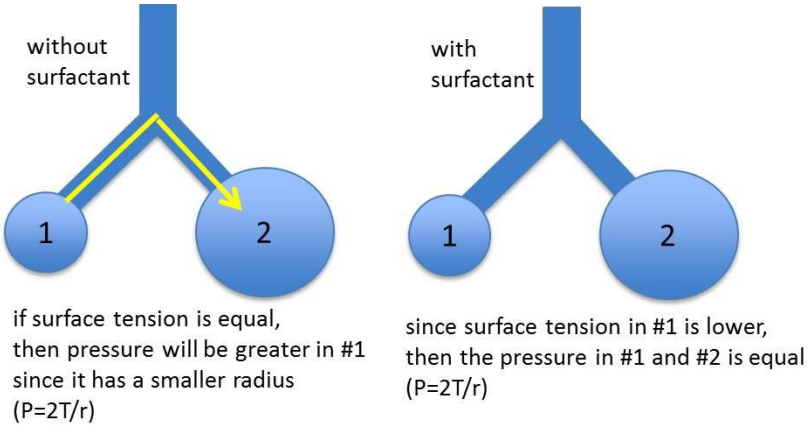

Figure 6. Stabilizing effect of surfactant on lung alveoli.

According to Laplace, transmural pressure is equal to twice the surface tension divided by the radius:

Transmural Pressure = 2T/r

If surface tension were equal in alveoli of different sizes, the pressure in the smaller alveolus would be greater than the pressure in the large alveolus and the smaller alveolus would collapse into the larger one.

Alveolar collapse does not normally happen because the surface tension in a lung with surfactant is not constant. Instead **surfactant reduces surface tension in a nonlinear fashion**; i.e., as area is reduced, surface tension is reduced even further. By lowering surface tension proportionately

more in smaller alveoli, surfactant makes it possible for alveoli of different radii to coexist and to be stable at low lung volumes.

During normal tidal breathing, the surface area of the lung remains fairly constant and with time the surfactant becomes "inactivated" through poorly understood mechanisms. A deep sigh or a yawn will increase the surface area of the lungs and new surfactant will spread at the air-liquid interface.

3. Pressure changes and resistance

Pressure Changes Affect Lung Volumes

In a normal lung, air flows in and out when a pressure gradient is created. Gas always flows from a higher to a lower pressure. During inspiration, expansion of the thorax causes the intrapleural and alveolar pressures to decrease, gas flows into the lung. During exhalation passive recoil of the lung causes the intrapleural pressure and alveolar pressure to increase; gas flows out of the lung. **Note that during inspiration and exhalation the pleural pressure is always less than the pressure in the alveoli.**

The transpulmonary pressure (Fig. 7) also increases and decreases with lung volume. By convention, the transpulmonary pressure is always positive ($P_{tp} = P_A - P_{ip}$).

At the end of an unforced exhalation when no air is flowing, then the following conditions exist:

alveolar pressure = 0 mmHg
intrapleural pressure (i.e., pressure in pleural cavity) = -5 mmHg
transpulmonary pressure ($P_A - P_{ip}$) = +5mmHg.

When there is no airflow in or out of the lungs, the transpulmonary pressure and intrapleural pressure are **equal in magnitude but opposite in sign** (Fig. 7).

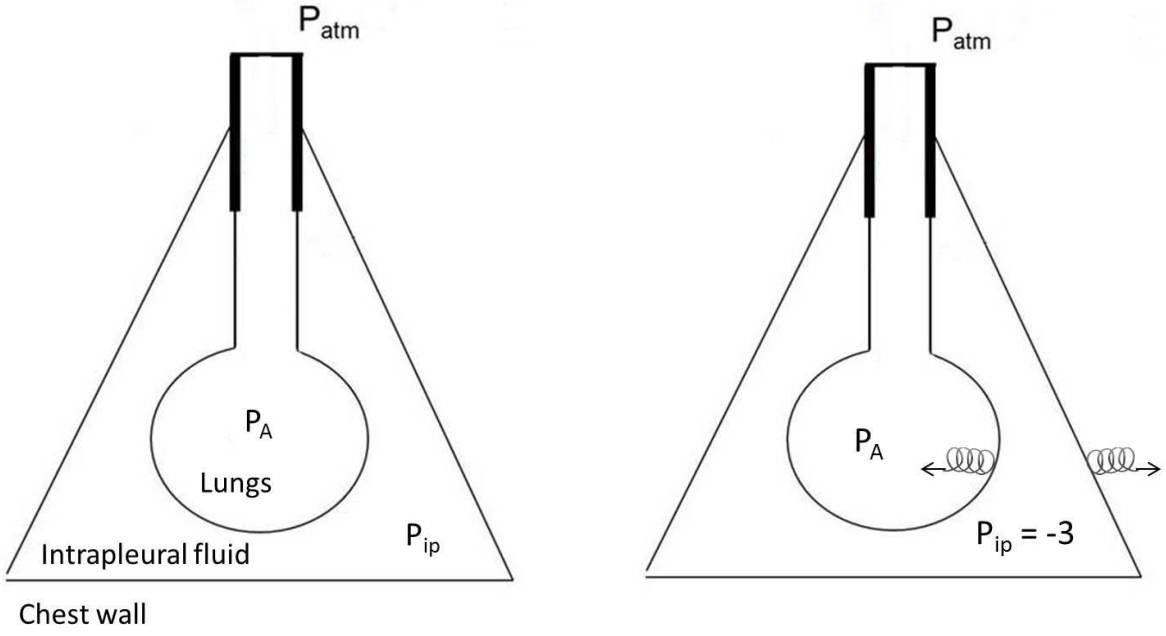

Figure 7. In ventilation, air flow is determined by the difference between atmospheric and alveolar pressures. Lung size is determined by the balance between the transpulmonary pressure and elastic recoil.

At rest, the volume of the lung is a balance between the expansion of the chest wall and the inward elastic recoil of the lungs. The lung at rest is in a partially expanded state (stretched). A **pneumothorax**, can occur with trauma or surgery. In this instance, the chest wall is pierced without damaging the lung. Atmospheric air enters the intrapleural space raising its pressure to 0 mmHg. This input of air causes the lung to collapse since its elastic recoil is no longer opposed. Concurrently the chest wall moves outward.

Airway Resistance Determined by Driving Pressure & Flow

Thus far we have discussed the changes in pressure that are required to overcome the elastic recoil tendencies of the respiratory system. An additional force that must be overcome during normal breathing is the **resistance to airflow**. Measurement of airway resistance is an extremely useful diagnostic tool because changes in airway resistance accompany aging and many lung diseases.

Air flow (F) will depend upon the driving pressure (P) and the resistance (R) according to the equation:

$$F = (P_{atm} - P_{A)}/R$$

Factors that influence airway resistance include airway diameter, lung volume, and elastic recoil of the lung.

1. AIRWAY DIAMETER: It is probably intuitive that the more narrow the airway, the higher the resistance in that individual airway. What may not be intuitive is that most of the resistance to air flow is found in the mouth, trachea and large bronchi. The reason for this is that as the airways divide and become narrower, they also become more numerous. The small airways divide more rapidly than their diameter decreases, therefore, the resistance of each individual airway is relatively high, but their total-cross sectional area is so great that their combined resistance is low.

2. LUNG VOLUME: The diameter of the airway lumen is affected by lung volume. The airways are not rigid and are capable of being distended and compressed. At high lung volumes, the airways such as bronchi and bronchioles, are "pulled" open and their resistance is lower than at low lung volumes. Patients with increased airway resistance frequently have high lung volumes in an attempt to compensate.

3. ELASTIC RECOIL: Airway diameter will be affected by the transmural pressure across them (Fig. 8). Although the airways are embedded in the lung, the pressure that they are exposed to on their outside wall is close to intrapleural pressure. If elastic recoil is reduced, then intrapleural pressure will be less negative than normal. The transmural pressure across the airways will be reduced, the airway diameter will be smaller than normal, and resistance will be higher than normal. Patients with emphysema often have destruction of lung tissue, decreased elastic recoil (increased compliance), and increased airway resistance.

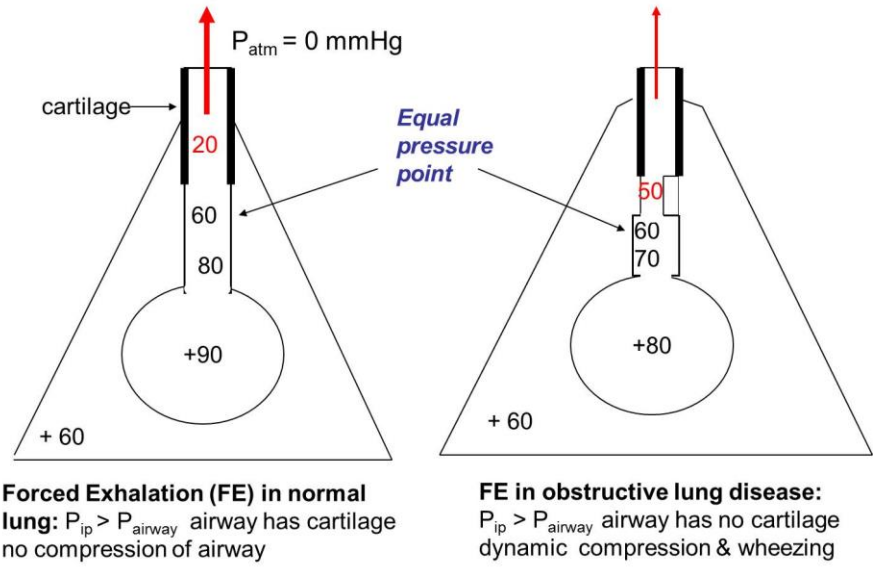

Figure 8. Increased resistance in the airways (bronchi) can lead to airway compression. The movement of air through the narrowed opening can cause wheezing.

At the **equal pressure point,** pressure inside the airway equals that in the pleural space. In normal lungs this occurs in the large airways which are surrounded by cartilage. However, in diseases associated with airway obstruction, resistance to flow is increased and the pressure gradient for flow is reduced. Consequently the **equal pressure point** moves into airways that do not contain cartilage causing these airways to close completely (premature airway collapse) (Fig. 8). This premature airway closure can be heard as **crackles**.

4. MUSCLE TONE Constriction of bronchial smooth muscle will decrease the diameter of the airways and increase airway resistance. **Parasympathetic stimulation causes contraction of bronchial smooth muscle; sympathetic stimulation causes relaxation**. Asthmatics often have hyper-reactive airways and smooth muscle contraction. Drugs which stimulate β-adrenergic receptors (βAR) in the bronchioles cause relaxation and are often used to treat asthmatics.

4. Pulmonary function tests and alveolar ventilation

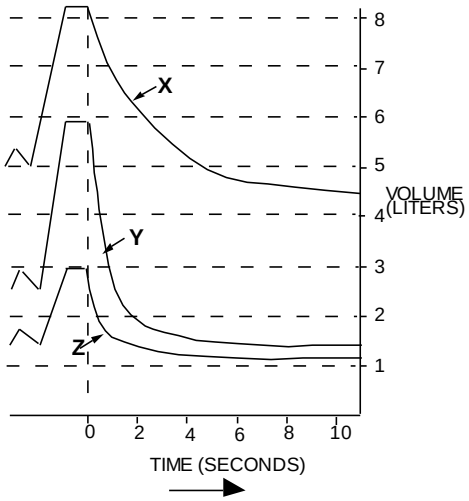

Figure 9. Forced expiratory vital capacity curves generated by individuals X, Y and Z.

FORCED EXPIRATORY VITAL CAPACITY TEST provides an indirect assessment of airway resistance. In this pulmonary function test, the subject inhales to total lung capacity and then exhales into a spirometer as forcefully, rapidly, and as completely as possible. The volume expired under these conditions is called the **forced vital capacity** (FVC) (Fig. 9).

The forced expiratory vital capacity test also measures the volume exhaled in 1 second, called the **1-second forced expiratory volume** (FEV1). This value is often expressed as a % of FVC (i.e., FEV1/FVC %). Normally FEV1 is at least **80% of FVC** (curve Y). Patients with restrictive lung disease will have a normal value of 80% (curve Z). In patients such as asthmatics, who have obstructed airways, this value will be reduced (<80%) (curve X).

Exchange of Gases in Alveoli & Tissues

Respiration involves two processes:

(1) Delivery of O_2 to and removal of CO_2 from the cells of the body.
(2) Use of O_2 in oxidative metabolism to generate ATP, water, and CO_2.

In a steady state, the amount of O_2 that is consumed by the cells per unit time is equal to the amount of O_2 added to the blood in the lungs during the same time period. Likewise the rate at which CO_2 is generated by the cells is equal to the rate at which CO_2 leaves the blood in the lungs and is exhaled.

Gases move by diffusion from regions of high concentration to regions of low concentration. Therefore to provide adequate gradients for diffusion, the pulmonary system must increase the amount of oxygen in the alveoli above that found in the mixed venous (MV) blood of the lung. Additionally it must lower the carbon dioxide in the alveoli below that of mixed venous blood.

A second set of gradients must exist at the tissue-blood interface. Here the amount of O_2 consumed by cells and CO_2 produced are not necessarily identical and depend on the fuel source consumed. The ratio of CO_2 produced to O_2 consumed is called the **respiratory quotient (RQ).** For a mixed diet, 8 molecules of CO_2 are produced for every 10 molecules of O_2 consumed (i.e., RQ = 0.8). For a diet composed of carbohydrates, the RQ is 1.0. For a diet of fat, the RQ is 0.7.

Minute & Alveolar Ventilation

Minute ventilation (V_E) is the total volume of gas entering (or leaving) the lung per minute. It is equal to the tidal volume (TV) multiplied by the respiratory rate (*f*).

Minute ventilation = $\mathbf{V_E = TV \times f}$

At rest, a normal person moves ~450 ml/breath x 10 breath/min = 4500 ml/min.

However, because of the anatomical dead space (V_D), not all of this entering air is available for exchange with the blood (Fig. 10). Recall that the conducting airway (anatomical dead space) has a volume of ~150 ml. As illustrated in figure 10, when 450 ml of fresh air is inspired, the first gas to reach the respiratory zone comes from this anatomical dead space (150 ml). Then 300 ml of fresh gas reaches the respiratory zone and the last 150 ml of inspired gas remains in the dead space. Thus, the total amount of fresh air reaching the alveoli during each inspiration equals the tidal volume minus the volume of the anatomical dead space:

$TV - V_D = 450 - 150 \text{ ml} = 300 \text{ ml}.$

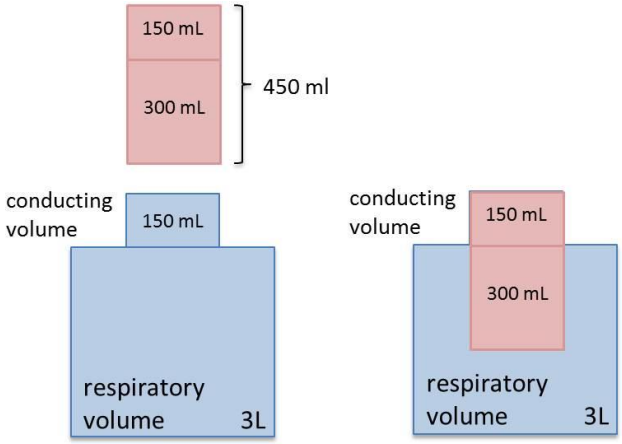

Figure 10. Effect of anatomical dead space on alveolar ventilation.

Alveolar ventilation (V_A) is the total volume of *fresh air* entering the alveoli per minute. It is calculated as:

Alveolar ventilation = $\mathbf{V_A = (TV - V_D) \times f}$

When evaluating the efficiency of ventilation, one should focus on the alveolar ventilation not minute ventilation.

For example, in the table below, Subjects A and B have the same minute ventilation (V_E = 6 L) but very different alveolar ventilations (V_A). Subject A has no alveolar ventilation and would be become unconscious in a few minutes but Subject B is breathing normally.

Subject	TV	*f*	V_E	V_D	V_A
A	150ml	40	6000ml	150ml	0
B	500ml	12	6000ml	150ml	4200ml

One other important point shown in the table above is that the **depth of breathing** (TV) is far more effective in elevating the alveolar ventilation than an increase in **ventilation rate** (*f*). This is because for each tidal breath a fixed volume is dead space. As tidal volume decreases, the fraction going to dead space increases. The respiratory system will respond to O_2 need (as in exercise) by reflexively increasing ventilation by **increasing the depth of breathing.**

The anatomical dead space is not the only type of dead space in the lung. Some fresh air is not used for gas exchange even though it reaches the alveoli because some alveoli may have little or no blood supply (i.e., blood perfusion). This volume of air is called **alveolar dead space**. In normal individuals this is quite small but may be large in several kinds of lung disease. As we will discuss later, a **mismatch in ventilation and blood perfusion** is minimized by local mechanisms that match air and blood flow. **The sum of the anatomical dead space and alveolar dead space is the physiologic dead space**.

Partial Pressure of Gases

The amount of various gases can be measured by comparing the pressure they exert. Gas molecules behave like individual particles that are in a constant state of motion. When the particles collide with one another or the sides of the container they exert a pressure. The pressure exerted depends on the number of collisions. Two factors affect the number of collisions: the **temperature of the gas** and the **number of gas molecules**. Dalton's law states that in a mixture of gases, the pressure exerted by each gas is the same as it would be if that gas alone occupied the entire container. These individual pressures are called **partial pressures** and are denoted as P in front of the symbol for the gas.

To calculate the partial pressure of gas "X":

$$P_X = P_{atm} \times F_X$$

Where, P_{atm} is the atmospheric pressure (at sea level = 760 mm Hg), and F_X is the fractional concentration of gas X.

Atmospheric air contains mostly nitrogen (79%) and oxygen (21% O_2) with trace amounts of CO_2 and other gases. Air also contains water vapor. At sea level, water vapor is 47 mm Hg. For simplicity, respiratory physiologists and physicians generally assume that room air is **always dry**. Since **21% of dry room air is oxygen**, the fraction of O_2 in inspired air (FiO_2) is:

$$\mathbf{FiO_2 \times P_{atm} = 0.21 \times 760\ mm\ Hg = 160\ mm\ Hg.}$$

The concentration of carbon dioxide in room air is so low (0.04%), it is considered to be 0.

When inspired, the room air is warmed to 37°C and becomes humidified as it passes through the nasal passages. The water vaporizes into the air until the P_{H2O}= 47 mm Hg. What this means is that only 760 - 47 mm Hg or 713mm Hg is available for other gases besides water. Therefore,

PO_2 of inspired gas = 0.21 X (760mm Hg - 47 mm Hg) = 150 mmHg.

5. Oxygen transport

Partial Pressures of Alveolar Gases

In the alveoli, the partial pressures of oxygen and carbon dioxide vary during the respiratory cycle. As gas exchange occurs, the alveolar partial pressure of carbon dioxide will rise and the alveolar partial pressure of oxygen will fall. Because these fluctuations are small (a few mm Hg) as compared with the 3000 ml present at the end of tidal exhalation, they are generally ignored and only **mean values PO_2 and PCO_2 are considered.**

The relationship between PO_2 and PCO_2 in the alveoli is described by the **alveolar gas equation**:

$$\mathbf{PAO_2 = (P_{atm} - P_{H2O}) \times FiO_2 - PACO_2/RQ}$$

Because diffusion is so rapid and complete in the lung, the $PACO_2$ and PAO_2 in the alveoli normally determine these gas pressures in arterial blood ($PaCO_2$ and PaO_2). But there is a slight difference between alveolar and arterial gas pressures even in normal subjects such that PAO_2 and PaO_2 differ by 5-15 mm Hg. This difference is due to anatomical shunting of blood (reduced perfusion) and to the mismatch between ventilation and perfusion that exists even in normal lungs. Both of these conditions will be discussed later in detail.

Normal values for **arterial PaO_2 and $PaCO_2$** are:

PaO_2 = 100 mm Hg
$PaCO_2$= 40 mm Hg.

The PaO_2 and $PaCO_2$ can be measured directly from arterial blood draws. PAO_2 is calculated by the alveolar gas equation. For a patient breathing room air at sea level, this equation simplifies to:

$$\mathbf{PAO_2 = 150 - PaCO_2/0.8}$$

Notice that alveolar PO_2 is determined by three factors:

1. PO_2 of atmospheric air
2. Alveolar ventilation rate
3. Rate of tissue O_2 consumption (RQ).

Each of these factors can change independent of another. For example, a decrease in either PO_2 of the atmospheric air (changes with altitude) or in alveolar ventilation (hypoventilation) will decrease the amount of fresh air entering the alveoli per unit time. Likewise, an increase in the rate of total body O_2 consumption will decrease PO_2 in the alveoli.

Because there is essentially no PCO_2 in inspired air, only the rate of ventilation and the rate of tissue metabolism affect the PCO_2 levels in the alveoli. In this instance, hypoventilation (Fig. 11) and/or increased cellular metabolism will increase PCO_2 in the alveoli.

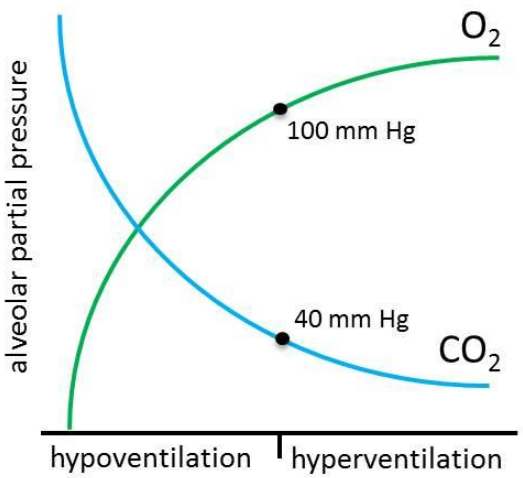

Figure 11. Effect of ventilation rate on PAO_2 and $PACO_2$. As ventilation increases, $PACO_2$ will decrease toward 0. As ventilation decreases, $PACO_2$ will increase.

Hypoventilation exists when there is an **increase in the ratio of CO_2 production to alveolar ventilation.** That is the alveolar ventilation cannot keep up with CO_2 production resulting in a rise in alvelolar **$PACO_2$ > 40 mm Hg** (Fig. 11). Hypoventilation can be caused by drugs such as barbiturates that depress the part of the central nervous system that drives breathing, or by damage to the chest wall, lungs, or respiratory muscles and when the movement of the chest wall is limited (e.g., caused by arthritis or deformation of the thoracic cavity).

Hyperventilation exists when there is a **decrease in the ratio of CO_2 production to alveolar ventilation**. That is the alveolar ventilation is too great for the CO_2 produced resulting in **$PACO_2$ < 40mmHg** (Fig. 11). Hyperventilation will occur in response to hypoxia, high altitude, or some drugs such as cocaine which can cause anxiety attacks.

***Notice that **hyperventilation is not the increased ventilation** that accompanies mild to moderate aerobic exercise. In aerobic *exercise the increase in production of CO_2 is matched to increased alveolar ventilation (depth and rate of breathing).*

Transport of Oxygen and Carbon Dioxide

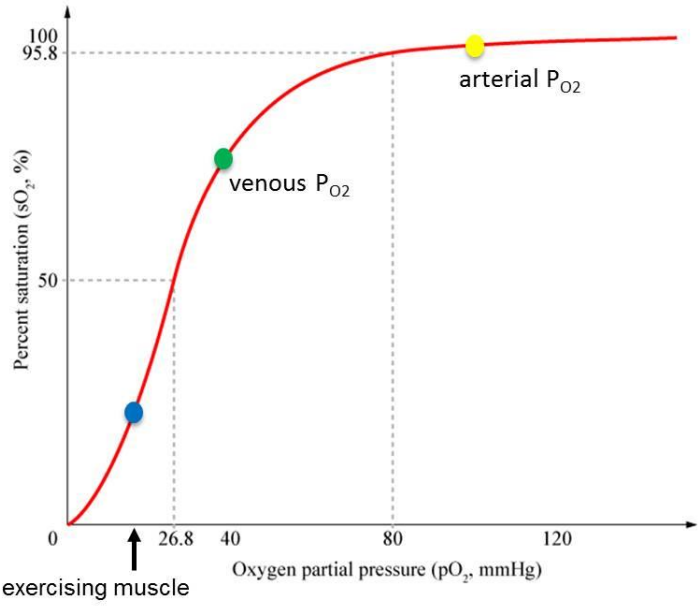

Figure 12. Hemoglobin dissociation curve. image by Diberri (modified), http://commons.wikimedia.org/wiki/File:Hb_saturation_curve.png, Creative Commons Attribution-Share Alike 3.0 Unported license.

To enhance delivery and transport of O_2 and CO_2 to and from tissues, specialized mechanisms (O_2-hemoglobin and bicarbonate transport of CO_2) have evolved.

OXYGEN TRANSPORT

Oxygen is not very soluble in water and therefore requires the carrier, hemoglobin (Hb), for transport in blood. Blood normally contains about 15 g of Hb per 100 ml. This effectively raises the solubility of O_2 from 3ml/L of plasma (blood minus the red blood cells) to 200 ml/L plasma. Since oxygen consumption ranges from 250 to 1500 L/min, this extra O_2 carrying capacity of Hb enables the heart and lungs to provide for the O_2 needs of the body.

Hemoglobin binds up to 4 molecules of O_2 tightly, cooperatively, and reversibly. Normally Hb is almost completely saturated (96%) when exposed to room air (FiO_2 = 21%). This occurs because of

the transit time (0.75 seconds) for the red blood cell through the alveolus-capillary unit and the rapid equilibration (0.3 seconds) for both carbon dioxide and oxygen within this region of the lung.

This rapid equilibration reflects the driving pressure for diffusion and the solubility of the gas. The driving pressure for diffusion of CO_2 in the alveolus-capillary unit is lower ($PMVCO_2$-$PaCO_2$ = 46 mm Hg - 40mm Hg = 6 mm Hg) than that for O_2 (PaO_2 - $PMVO_2$ = 100 - 40 = 60 mm Hg), but the solubility of CO_2 in plasma is much greater. The net result is that the rates of diffusion for CO_2 and O_2 are approximately equal in the alveolus-capillary unit. This means that in normal lungs **there is ALWAYS adequate time to saturate Hb with O_2 regardless of ventilatory rate.**

Oxygen concentration in the blood is dependent on the **Hb concentration** in the red blood cells, the number of red blood cells (**hematocrit**), and on the adequacy of **perfusion** of the lungs rather than on diffusion rate itself.

Not all of the O_2 bound to Hb is released in the tissues. At rest only about 25% of the O_2 in blood is released (Fig. 12). This provides a large driving force for diffusion and a large reservoir of O_2 to be called upon when needed as in exercise.

The Hb-O_2 dissociation curve (Fig. 12) is **S-shaped** because the interaction of oxygen with hemoglobin is **cooperative**. That is, when one oxygen molecule binds, it increases the affinity of the hemoglobin for the next oxygen molecule. Each hemoglobin molecule can bind four oxygen molecules.

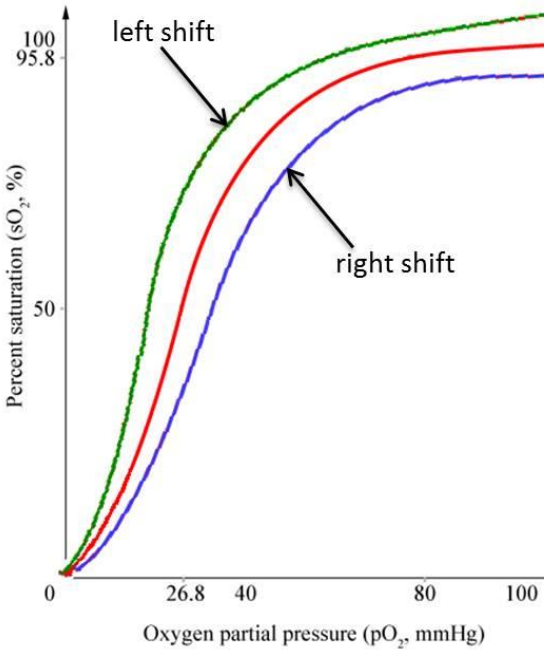

Figure 13. Shifted hemoglobin dissociation curve. image by Diberri (modified), http://commons.wikimedia.org/wiki/File:Hb_saturation_curve.png, Creative Commons Attribution-Share Alike 3.0 Unported license.

The plateau of the Hb-O_2 dissociation curve is called the "**association part"** of the curve, because oxygen is loaded in the lungs at relatively high partial pressures. Increasing the partial pressure above 100 or down to about 80 mm Hg, ***does not result*** in a large change in the % saturation. This tends to stabilize arterial O_2 content, making it relatively insensitive to moderate changes in breathing or altitude.

The "**dissociation part"** of the curve is the steep part of the curve (Fig. 12). In this region a small change in PO_2 results in a large change in % saturation which allows for large quantities of oxygen to be dumped in the tissues.

The P50 is the partial pressure of oxygen required to saturate 50% of the hemoglobin. A normal P50 is about 26-27 mm Hg. This value is a useful measure of the affinity of hemoglobin for O_2.

Oxygen-Hb binding and association is affected by a number of parameters including temperature, the red blood cell metabolite 2,3 diphosphoglycerate (DPG), and pH. Elevated temperature, low pH and increased 2,3 DPG shift the curve to the right (**decrease affinity**) which **enhances unloading of O_2 from Hb** (Fig. 13). Note that these are conditions found within

the interstitial tissue surrounding actively contracting muscle. Hypoxic conditions also result in increased formation of 2,3-DPG by the red blood cells.

Conversely, a decrease in temperature, high pH and a decrease in 2,3, DPG shifts the O_2-Hb dissociation curve to the left (**increase affinity**) which **promotes loading of O_2 onto Hb** (Fig. 13).

6. CO2 transport and V/Q mismatch

CARBON DIOXIDE TRANSPORT

Carbon dioxide is a product of oxidative metabolism. Unlike O_2, CO_2 is very **soluble in water** and does not need a carrier for transport in the blood. Most (60%) of the carbon dioxide in blood is transported as **bicarbonate (HCO_3^-)**. The conversion of CO_2 to bicarbonate is catalyzed by the enzyme carbonic anhydrase located inside red blood cells.

$$\mathbf{CO_2 + H_2O = H_2CO_3 = HCO_3^- + H^+}$$

Once formed, the HCO_3^- is transported out of the RBC into the plasma in exchange for Cl^-.

About 10% of the total CO_2 in blood is transported as dissolved CO_2. The amount dissolved is proportional to the PCO_2, and to the solubility coefficient for CO_2. At $PaCO_2$ = 40 mm Hg, there would be approximately 26.8 ml CO_2/L of plasma.

The remaining 30% of the CO_2 combines with Hb to form carbamino-hemoglobin compounds.

Because **CO_2 diffuses 20X more rapidly than O_2,** a rise in blood CO_2 can be compensated by an increase in ventilatory rate. **Hyperventilation increases the amount of CO_2 removed from the body and increases the unloading of CO_2 from the blood in the lung.**

Ventilation & Perfusion

Ventilation is the process of bringing air in and out of the lungs. Perfusion is the process of bringing blood in and out of the lung capillary bed to allow for gas exchange. The right ventricle delivers blood to the lungs at relatively low pressures (mean pressure of 15 mmHg). However, lung perfusion pressure can increase for multiple reasons including obstruction of vessels (i.e., embolism) or increased resistance to flow (i.e., fibrosis). The lung will compensate for lowered blood flow (1) by recruiting other capillary beds within the lung and (2) by distention of small vessels. If these responses are inadequate, then pressure within the pulmonary artery will rise causing a rise in right ventricular pressure. This is called **pulmonary hypertension**.

Under normal conditions, regulatory mechanisms within the lung **match ventilation (V) to perfusion (Q) to optimize the oxygenation of the blood.** V/Q mismatch can occur when ventilated alveoli are not perfused giving a V/Q ratio of infinity and conversely, when unventilated alveoli are perfused, giving a V/Q ratio of zero. This latter condition is equivalent to shunting venous blood from the right to the left side of the heart bypassing the lungs. Usually lung disease is progressive. It leads to a gradual worsening of either ventilation or perfusion and therefore the **V/Q mismatch** is intermediate between zero and infinity. Many believe that V/Q mismatching is the most common cause of low PaO_2.

In a normal individual at the level of the lung, alveolar ventilation is about 4.0 L/min and pulmonary blood flow is about 5.0 L/min. This gives a V/Q = 0.8 overall.

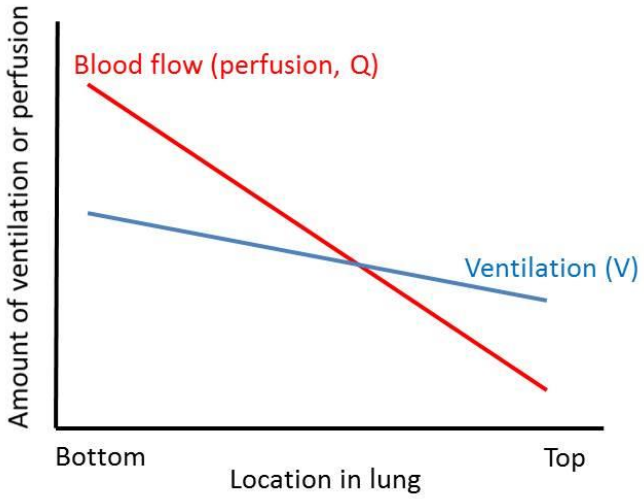

Figure 14. V/Q mismatch in a normal lung.

Note that **V/Q mismatch** occurs within the normal lung because blood flow is never perfectly uniform in this organ. In a normal person while standing, gravitational pull causes the apex of the lung to be more expanded than within the base thereby compressing the capillaries and reducing perfusion; V/Q ratios are greater than 1 in the apex (Fig. 14). In contrast, perfusion is greater than ventilation at the base of the lung in an upright individual; V/Q ratios are less than 1 (Fig. 14).

One mechanism that compensates for V/Q mismatch is the **vasoconstriction of the lung vasculature in response to hypoxia (low O_2).** [Note that this is in contrast to the smooth muscle of the systemic vasculature which dilates in response to low O_2 conditions.] **Vasoconstriction of the lung vasculature to hypoxia** enables the blood to be shunted away from poorly ventilated areas. This occurs without an increase in pulmonary artery perfusion pressure because of the large capacity of the pulmonary capillaries.

A second compensation that compensates for V/Q mismatch occurs when $PACO_2$ falls (e.g. when V/Q ratio increases). In this instance, the concentration of hydrogen ions (H+) in and around the smooth muscle of the airways (bronchioles) decreases. This reduction in H+ results in airway constriction and a shift of ventilation away from the areas which are over ventilated (i.e., not perfused).

7. Regulation of breathing

Control of Respiration

Breathing is essentially automatic and can only be altered temporarily by voluntary efforts. You cannot consciously stop breathing for long. You breathe when you are asleep, awake, or even anesthetized. Breathing is finely tuned to meet metabolic demands, such that during exercise ventilation increases to maintain arterial PO_2, PCO_2 and pH within a narrow range. To achieve this tight regulation, peripheral receptors send information to a CNS respiratory center whose output adjusts initiation, duration, depth, and rate of breathing.

The intercostal muscles and diaphragm are skeletal muscles that will not contract unless stimulated. Thus breathing depends on cyclical excitation of the motor neurons that innervate these muscles. Destruction of these nerves by the polio virus for example results in paralysis and death if the individual is not ventilated.

The underlying respiratory rhythm is established by **respiratory centers** in the **medulla of the brain stem**. The general term for this integration center is the **respiratory rhythm generator**. Inspiratory neurons located in the respiratory center initiate respiratory rhythm by sending signals to the motor neurons that innervate the effector skeletal muscles (intercostals and diaphragm). This rhythm is modified by input from **peripheral sensors** (**chemoreceptors and mechanoreceptors)** located in blood vessel walls and by central receptors (chemoreceptors) in the brain.

Inspiration is limited by several inputs including stretch of the lungs and innate rhythm generators within the brain stem (medulla). The medullary inspiratory neurons are quite sensitive to drugs such as barbiturates and morphine. Death from an overdose of these drugs is often due to cessation of breathing.

Inspiratory receptors in the lung include:

1. Pulmonary stretch receptors located in the smooth muscle of the large and small airways of the lung are mechanoreceptors that fire with the inflation of the lung. These receptors **stop inspiration** as part of the **Hering-Breuer reflex**. In the adult this reflex is evoked only under conditions of large tidal volumes as in rigorous exercise.

2. J Receptors located in the walls of the pulmonary capillaries which are stimulated by pulmonary vascular congestion, edema, air emboli (air in the blood), and low lung volumes. Stimulation of these receptors can result in **rapid breathing** (**hyperpnea)**, and or labored breathing (**dyspnea).**

3. Pulmonary irritant receptors located in airway epithelium and the nasal mucosa. Mechanical or chemical irritation elicits a **cough reflex** and **bronchoconstriction**.

Transport of Hydrogen Ions

Metabolism generates protons (H+) which are extruded to the interstitial fluid surrounding cells and eventually enter the blood by diffusion. As blood flows through the tissues, a fraction of the oxy-hemoglobin (O_2-Hb) loses its oxygen to become deoxy-Hb. Deoxy-Hb has a much higher affinity for H+ and thus binds most of the newly generated H+.

$HbO_2 + H+ = HbH + O_2$

This effectively removes the H+ from the blood and thereby buffers the blood. As a consequence venous blood is slightly more acidic (pH of 7.36) than arterial blood (pH 7.4).

As venous blood passes through the lungs, HbH is converted to HbO_2 and H+ is released. The H+ reacts with the bicarbonate (HCO_3-) in the blood to give carbonic acid (H_2CO_3) which dissociates to $H_2O + CO_2$. The CO_2 diffuses into the alveoli to be expired. **Normally all of the H+ will be removed** by this process and none will appear in the arterial blood.

$H+ + HCO_3- = H_2CO_3 = H_2O + CO_2$

However, if an individual is either **hypoventilating** or has a lung disease that prevents normal elimination of CO_2, then the $PaCO_2$ will rise and the arterial H+ concentration will rise (by mass action). Increased arterial H+ concentration due to CO_2 retention is called **respiratory acidosis.**

Conversely, if a person is **hyperventilating,** then $PaCO_2$ and H+ concentration will decrease, producing **respiratory alkalosis**.

Ventilation is Regulated by Chemoreceptors

Respiratory rate and tidal volume can increase or decrease over a wide range. At rest, chemoreceptors located in the periphery and centrally within the CNS provide feedback to regulate these two factors.

Peripheral chemoreceptors are the carotid receptors and aortic bodies. They are stimulated by:

a. decrease in PaO_2 (hypoxia)
b. increase in $PaCO_2$ (respiratory acidosis)
c. decrease in pH within the arterial blood (metabolic acidosis).

Of the two, the **carotid receptor is the predominate input** in controlling respiration.

Central chemoreceptors are widely distributed throughout the brain stem. They **respond to an increase in blood PCO_2. These receptors actually sense H+ concentration in the interstitial fluid of the brain.** They are not affected by changes in arterial pH because the blood brain-barrier is not permeable to H+ or HCO_3-. Instead, CO_2 equilibrates across this barrier, causing a change in the interstitial fluid pH. Because the interstitial fluid and the adjoining cerebrospinal fluid contain little protein, they are not well buffered. Hence **small changes in PCO2 produce large changes in pH in this area**.

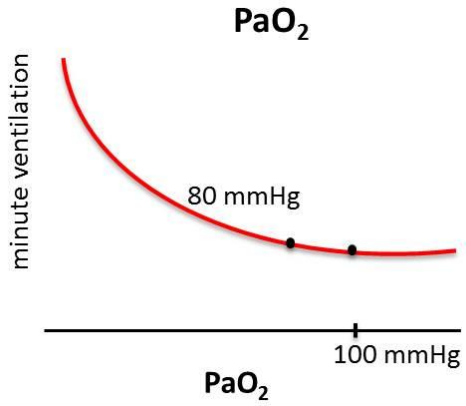

Figure 15. Effect of low arterial O_2 pressures on ventilation

Ventilatory Response to Oxygen

The ventilatory response to hypoxia is shown in the graph below (Fig.15). PaO_2 must decrease to about 50-60 mm Hg before respiration is increased. It has been suggested that the carotid chemoreceptors (which respond to changes in PaO_2), are designed to protect the organism against hypoxia rather than to regulate respiration. Note that the stimulation to hypoxia is **arterial PO_2 not arterial O_2 content**. That means that individuals **with anemia do not have increased ventilation** because their PaO_2 is normal.

Ventilatory Response to Carbon Dioxide

A very small increase in $PaCO_2$ (2-4 mm Hg) provides a powerful stimulus to increase respiration (doubles alveolar ventilation) (Fig. 16). What is the physiologic role of this response? Recall that changes in $PaCO_2$ have profound effects on pH. Thus this tight regulation of $PaCO_2$ allows for tight control of acid-base balance. For example, in emphysema patients retention of CO_2 occurs because of the decrease in the elastic recoil. This raises their $PaCO_2$ leading to increased minute ventilation (i.e, "blowing down" the CO_2 in the blood). Of the two sets of receptors involved in this reflex response to elevated $PaCO_2$, the central chemoreceptors are more important accounting for ~70% of the increased ventilation.

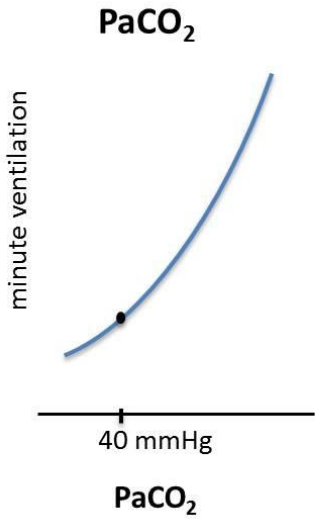

Figure 16. Effects of arterial PCO_2 on minute ventilation.

Hypoxia (low PO_2) potentiates the effects of CO_2. The response curve is shifted to the left and has a steeper slope. Thus a lower PaO_2 will result in a stronger ventilatory response for the same arterial PCO_2.

Very high levels of carbon dioxide (greater than 70-80 mm Hg) can depress respiration, cause headaches, restlessness, faintness, and even unconsciousness or coma.

Changes in pH without changes in $PaCO_2$

Excess retention or elimination of CO_2 causes respiratory acidosis or alkalosis, respectively. However, many normal and pathological conditions can change arterial H+ levels in which the primary cause is not a change in PCO_2. These conditions are called **metabolic acidosis** (increased H+ concentration) and **metabolic alkalosis** (decreased H+ concentration). Which chemoreceptors play a major role in these instances, central or peripheral? Why?

For example, in strenuous exercise, lactic acid is released by the working muscle. The addition of lactic acid to the blood lowers the pH and causes hyperventilation almost entirely by stimulating the peripheral chemoreceptors. Recall that H+ do not cross the blood brain barrier, but CO_2 does and is converted in the interstitial fluid to H+ and HCO_3-.

Predict what happens when arterial H+ concentration is decreased by vomiting (loss of acid from the stomach). Is ventilation increased or decreased? *Answer: The peripheral chemoreceptors will reflexively decrease ventilation to conserve CO_2 in the blood.*
Thus the respiratory system compensates for metabolic acidosis by increasing ventilation (hyperventilation) and for metabolic alkalosis by decreasing ventilation (hypoventilation). Notice that maintenance of PCO_2 levels is not as important as maintenance of H+ concentration in the blood. This is because most enzymes of the body function best at physiological pH (pH = 7.4).

8. Exercise and hypoxia

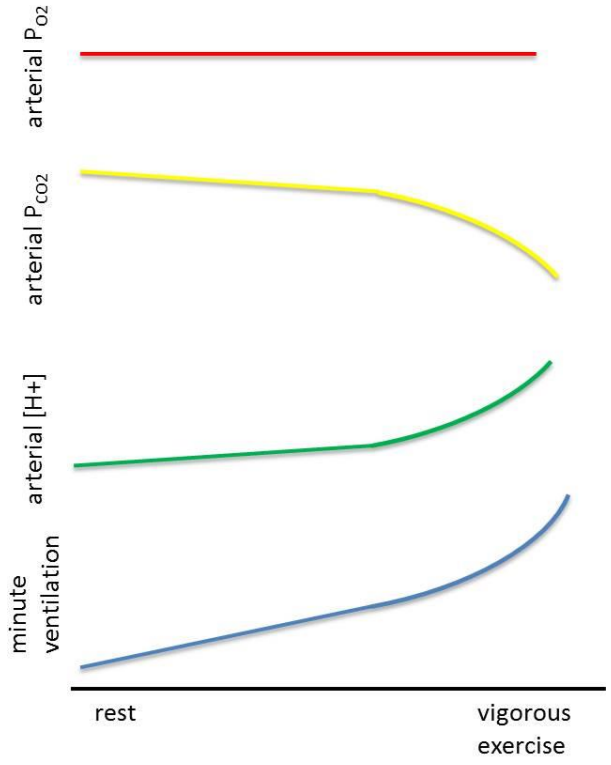

Figure 17. Effect of exercise on ventilation, arterial gas pressures and arterial H+ concentration.

Exercise Affects Ventilation

With moderate physical activity, both oxygen consumption and carbon dioxide production increase. Minute ventilation can increase up to 25-fold. It would seem logical to guess that the increase in CO_2 production increases $PaCO_2$ which would, in turn, stimulate ventilation. However, measurements of $PaCO_2$ during moderate exercise show that it does not change appreciably (Fig. 17). In fact, neither does PaO_2 nor pH (Fig. 17). However, at near maximal exercise, arterial H+ concentration does rise and $PaCO_2$ falls. Why does the H+ concentration increase while $PaCO_2$ decreases?

The mediators that cause increased ventilation in response to moderate exercise are likely to include increased body temperature, increased epinephrine level, reflex input from the mechanoreceptors of the joints and muscles, and conditioned behavior (feed forward).
The deep breathing after exercise removes the oxygen debt restoring oxygen storing molecule (myoglobin) and energy storing (creatine phosphate) in the muscles, as well as removing lactic acid and H+.

Hypoxia (Low PO_2) & Ventilatory Control

Hypoxia is defined as a deficiency of oxygen at the tissue level. There are many causes of hypoxia but they can be grouped into four classes.

1. ***hypoxia- hypoxia*** in which arterial PO_2 is reduced.
2. ***anemic hypoxia*** in which arterial PO_2 is normal but the content of O_2 is reduced because of inadequate numbers of red blood cells or incompetent Hb or competition of carbon monoxide for Hb.
3. ***ischemic hypoxia*** in which blood flow to the tissues is too low.
4. ***histotoxic hypoxia*** in which the O_2 content in the tissue is normal but the cell is unable to utilize it because a toxic agent (such as cyanide) interferes with oxidative metabolism.

Individuals who reside at high altitudes (where O_2 tension is reduced) or who have sleep apnea syndrome (that is, they stop breathing for prolonged periods during sleep) may have diminished hypoxia drive to breathe. This is due to the "resetting" of their chemoreceptors set point.

The effects of O_2 deprivation vary from individual to individual but most people who ascend rapidly to altitudes above 10,000 ft experience some degree of ***altitude sicknesss***. The symptoms of altitude sickness are headache, nausea, vomiting, fatigue and possible mental confusion. In severe cases, life threatening pulmonary edema can occur due to pulmonary hypertension. Over a course of a several days these symptoms will disappear due to acclimatization which includes increased hematocrit (more red blood cells), increased 2,3, DPG and a shift in the O_2 dissociation curve to the right to facilitate unloading in the tissues.

During sleep, breathing frequency and inspiratory flow rate are reduced and minute ventilation decreases. This is accompanied by a relaxation of the skeletal muscle tone throughout the body including those muscles associated with the larynx, pharynx and tongue. Relaxation of muscle tone in these areas can cause partial obstruction of the upper airways and **snoring**. However, in some individuals the airways are completely occluded which can lead to **sleep apnea**. In sleep apnea, respiration stops for long periods (30-60 sec) and $PaCO_2$ rises; the respiratory center is stimulated. The individual reacts by gasping and often awakens.