Section Three: Chapter 18: Respiratory Physiology

Although breathing may not be something we think about often, we are doing it all the time. To put things in context, think of this: It is said we can live without food for about **40 days**, live without water for about **4 days** and live without breathing for about **4 minutes**. These times of course are all dependent on the circumstances and conditions, but the point is that breathing, like the heartbeat, needs to be constant throughout our lives or we won't be alive for very long. Also like the heart, the pattern (rate and depth) of breathing is constantly changing to meet the needs of the body.

The respiratory rate (number of breaths per minute) of a healthy person normally ranges from 12 to 20 breaths per minute for an adult at rest. On average, that is a rough estimate of about **20,000** breaths a day. Thank you lungs and entire respiratory system!

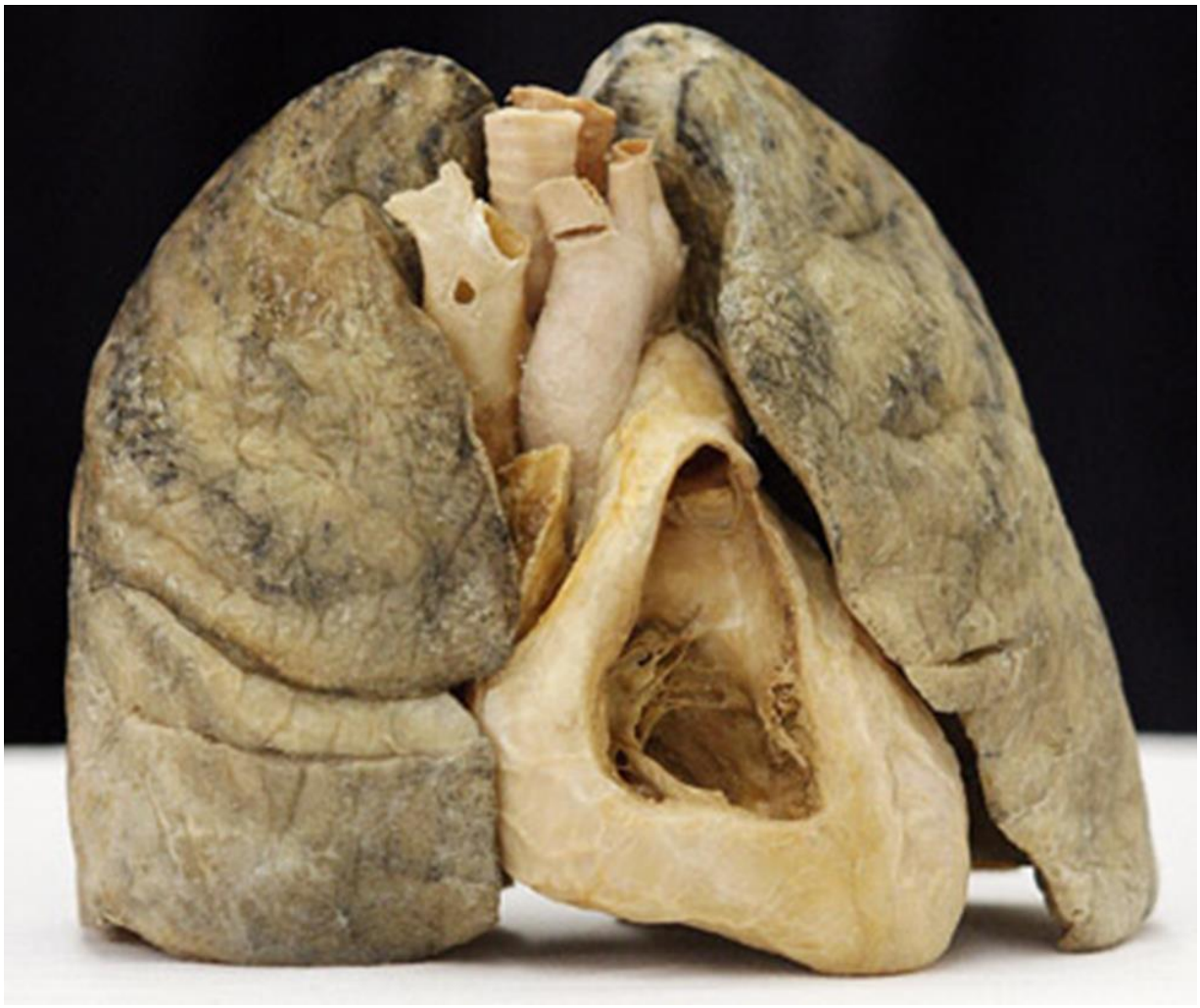
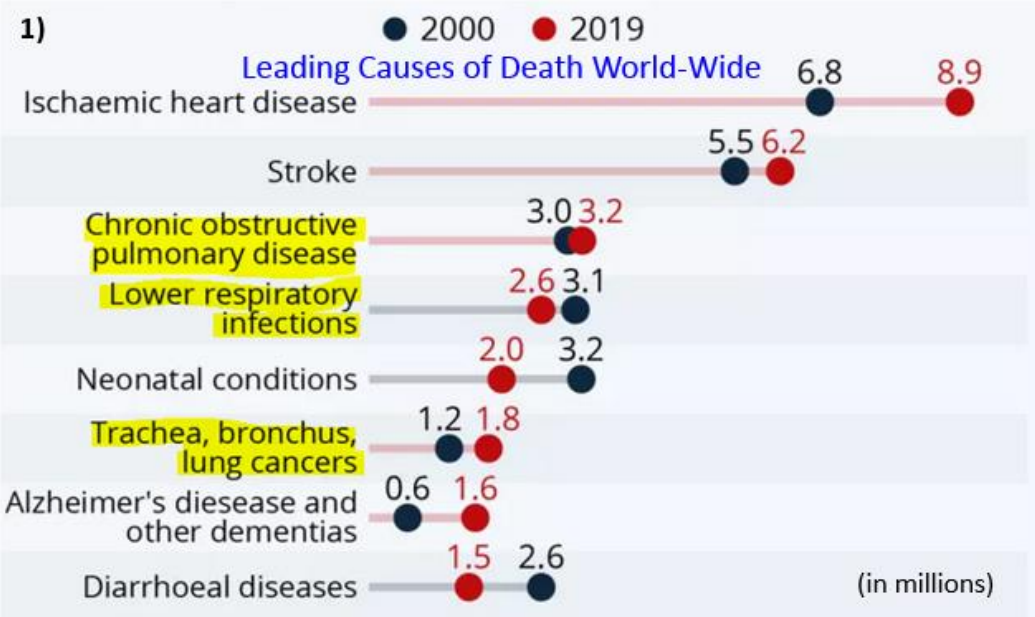


Figure 18.1. This is a photo of a human heart and lungs specimen. The tissue has been preserved by a method of plastination whereby water and fat are replaced with plastics, yielding specimens that can be touched, do not smell or decay, and even retain most properties of the original sample.

From the image in **Figure 18.1** above the anatomy reveals that the heart and the lungs have a very intimate and integrated functional relationship with each other. Their close proximity has important impacts on how they function.

The Importance of Lung Health

Just as a gentle reminder, below in **Figure 18.2** are two graphs of recent data regarding the leading causes of death both **1)** world-wide, and **2)** in the United States. The direct respiratory related deaths are highlighted in yellow and it illustrates the importance of maintaining not only healthy lungs, but entire body health.



For graph **1)** the combined respiratory ailments for 2019 were a total of about 8.1 million, effectively making it the #2 killer! For graph **2)** looking at the leading causes of death in the U.S., it shows respiratory deaths were far below heart disease and cancer for 2019, however, the cancer category also contains lung cancer.

A few interesting observations when comparing the two graphs. One is that they share the same #1 health problem, and that is cardiovascular or heart disease. A bold difference between the two sets graphs is the dominance of cancer in the United States as a cause of death, at #2. The only mention of cancer in the world wide stats is to do with those cancers directly linked with the respiratory system.

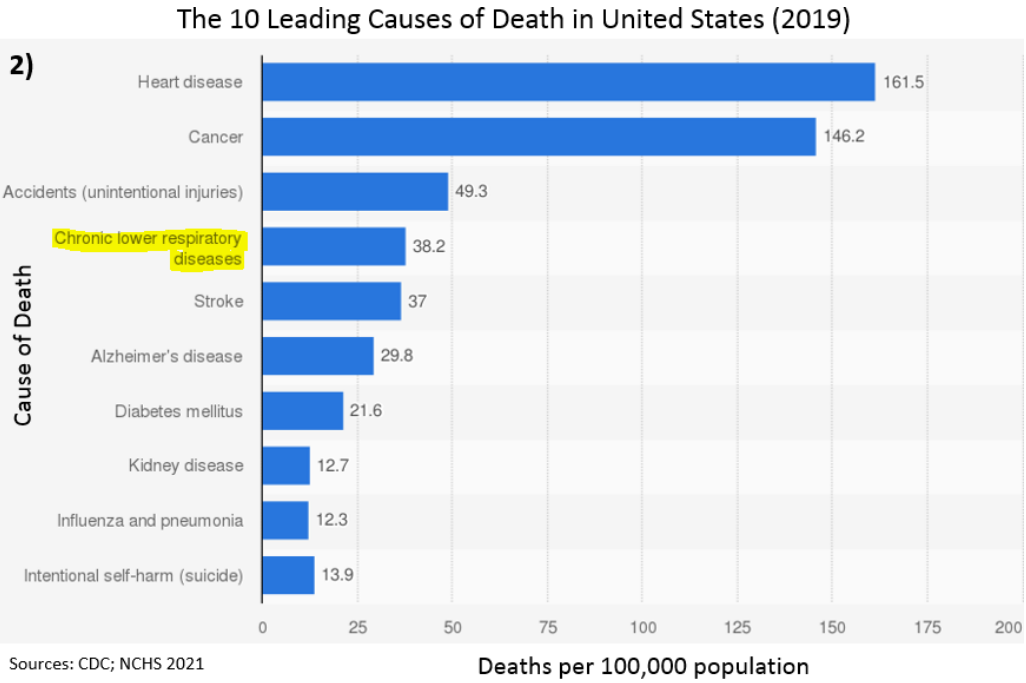


Figure 18.2 The two graphs above display recent data regarding the leading causes of death for both **1)** world-wide (numbers given in millions), and **2)** in the United States (numbers given per 100,000 in population). Highlighted in yellow on both graphs are those deaths related to disease of the respiratory system. Collectively they represent a significant number of deaths worldwide and in the United States.

Overview of the Respiratory System

The respiratory system is comprised of the **respiratory tract** which starts at the **nose** and includes all of the airways that terminate in the **alveoli** within the **two lungs** (left and right). Each of the lungs are contained within a **pleural sac** surrounding the lungs in a protective fluid filled pleural cavity that is situated within the **thoracic cavity**, which is protected by the ribcage.

The Various Functions of the Respiratory System

At first glance, it may seems as if the functions of the respiratory system would be simple and somewhat limited. Bring air in to the body, get the oxygen (O_2) from it, breath air out with some carbon dioxide (CO_2) in it. In a way its functions are very straightforward. At the same time, the processes are very involved and include a few physiological issues we have not covered extensively yet, like the inverse relationship between volume and pressure in the thoracic cavity, or the issues of partial pressures of a gas in the body. There is also an extremely integrated relationship between the respiratory system and the cardiovascular system that is fascinating and complex.

Main Pulmonary Functions:

1. **Ventilation:** Ventilation is the exchange of air between the body and environment. It involves inspiration (or inhaling) which brings in air from the atmosphere into the lungs; and Expiration (or exhaling) which pushes air from the lungs into the atmosphere. In the same way a room is ventilated by having air flow through it, the respiratory system ensures that air is constantly flowing into and out of the lungs.

2. **Exchange of Gases:** The lungs provide an enormous surface for gas exchange in the body. It is estimated that if the surface area of the two lungs combined (the left and the right) were unfolded and made a flat single layer, they would have an area comparable to the size of a tennis court. The terminal (end) structure in the lungs for gas exchange called the **alveoli** (singular alveolus). This location is where the **oxygen (O_2)** from the inspired air moves into the **pulmonary capillaries**, and the **carbon dioxide (CO_2)** produced by every healthy body is moved from the pulmonary capillaries into the alveoli.

3. **Maintenance of Acid-base Balance:** A critical role of the respiratory system is homeostasis of the **pH of body fluids**. The bicarbonate buffer system involves the **CO_2 levels in the body**, and by simply changing the breathing patterns (rate and depth of breathing), the pH of the body fluids is regulated.

4. **Phonation (Vocalization) and Sound Production:** Phonation is the production of a **voice**. It involves a power source (lungs and diaphragm), an oscillator (the vocal folds or chords inside the larynx), and resonance chambers (the nasal, sinuses and oral cavities).

5. **Protection:** Dust, toxins and microbes can enter the body via the respiratory tract and can cause damage. **Coughing** is an important reflex that can expel irritants and protect the lungs. Most of the respiratory tract is lined with **cilia**, tiny hair-like projections that propel sticky mucus that traps debris in the airways, and moves it back up to be spat out or swallowed.

6. **Olfaction and Taste Enhancement:** The senesce of smell (olfaction) relies on the movement of volatile particles in the air into the nasal cavity to cranial nerve II. The sense of taste (gustation) discrimination is reliant on olfaction, and dependent of the respiratory system.

Structures of the Respiratory System

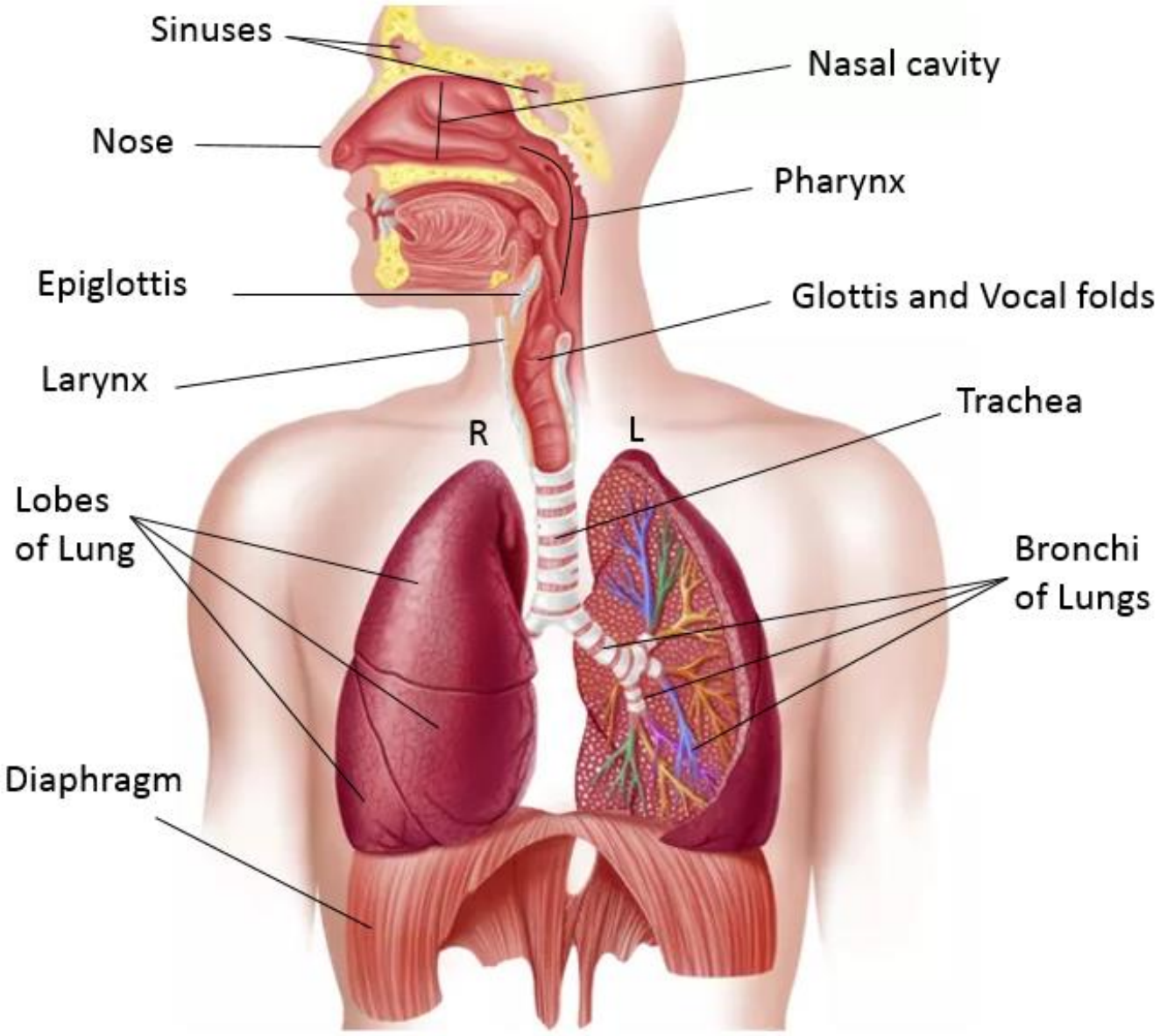


Figure 18.3 Here is the respiratory system from the point of entry/exit (nose) into the respiratory tract down to the branching air passages of the bronchi of the lungs. Also shown are two of the four paranasal sinuses and the large dome shaped diaphragm which is the primary muscle of respiration.

The Respiratory Tract

The Respiratory System includes structures involved in ventilation and gas exchange, see **Figure 18.3** above. The respiratory system is divided into **upper** and **lower** tracts, as well as **conduction** and **respiratory** portions. Since the respiratory tract begins at the openings of the nose, called the nostrils or nares, this is where our basic outline of the anatomical structures of the respiratory tract begins. As will be discussed later in the chapter, the large dome-shaped muscle called the diaphragm (seen at the base of the lungs in **Figure 18.3**) is the engine for inspiration, the contraction of which draws air into the lungs along the respiratory tract.

Tracing the Pathway of Air

It is useful to become familiar with the order of the respiratory tract and to examine the specific roles of the various regions. There is a type of compartmentalization in the respiratory system that allows some regions to have very specific functions that are different to other nearby areas. For the upper and lower respiratory tract let's examine the path and order that inspired air would move.

Upper Respiratory Tract

The upper respiratory tract is composed of these structures in this order (tracing the pathway of inspired air): *Nose -> external nares (nostrils) -> nasal cavity -> pharynx (throat) -> larynx (voice box)*. If someone says they have an inflamed upper respiratory tract, then it is one of these areas.

Function of Upper Respiratory Tract

The upper respiratory tract provides passage for air to be breathed in and out of the lungs. It also has a very critical role of **conditioning** the inspired air. The inspired air is conditioned in three ways: It is **1)** heated (up the body temperature); **2)** it is humidified (water vapor is added); and **3)** it is filtered of debris and particles. The vast majority of the conditioning of inspired air occurs in the **nasal cavity**.

Nose hairs act as a broad filter for large particles and the mucus lining traps errant debris. A key structure within the nasal cavity are the scroll-shaped **nasal conchae bones**, also called **turbinate bones**, because like a turbine engine they create turbulent air flow. There are three separate turbinate bones: the **superior**, **middle**, and **inferior** nasal conchae. They are covered by soft tissue (mucosa) and have a rich blood supply. The passages in between the bones are called **nasal meatuses** and this is where air flows with increased turbulence. This causes the flow of air to swirl and slow down which provides greater time in the nasal cavity to fully condition the air in preparation for it moving to the delicate and controlled environment of the alveoli at the very end of the tract.

Oscillatory Swelling of Nasal Cavity

The mucous membrane covering the turbinate bones have a rich supply of superficial blood vessels. This provides the heat and water vapor for conditioning inspired air. This tissue normally swells in order to effectively warm and humidify the passing air, however they are regulated to do so in an oscillatory fashion, swelling only one side at a time in order to prevent restricting the entire nasal cavity which can make it difficult to breathe. We probably all know the how much easier it is to breathe through the mouth compared to the nose (especially when running), this nicely exhibits how much the air is slowed in the nasal cavity.

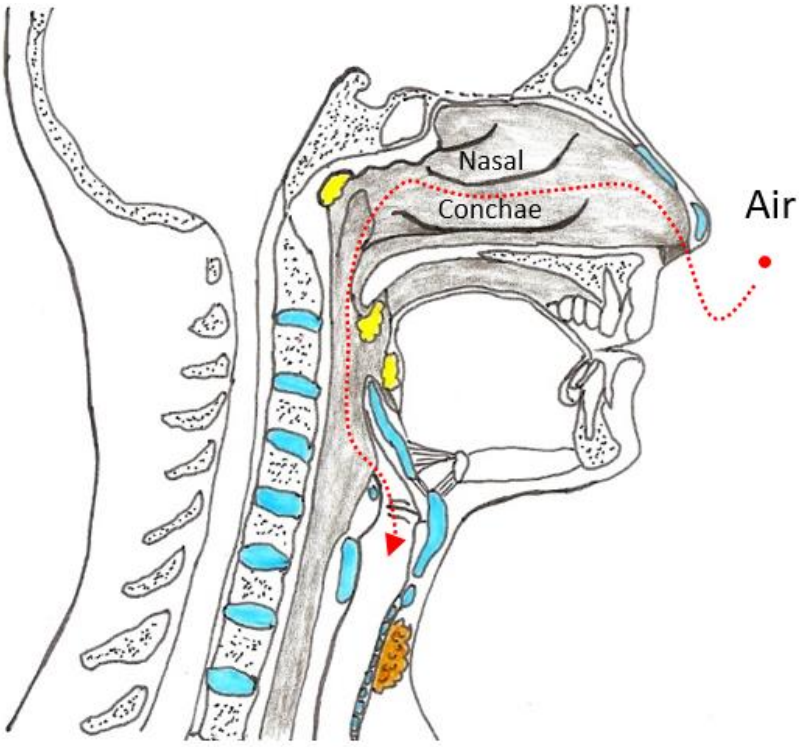


Figure 18.4 Diagram showing the movement of air during inspiration through the upper respiratory tract from the environment into the nose, through the nasal conchae, the pharynx and into the larynx (voice box).

Lower Respiratory Tract

The lower respiratory tract starts where the upper respiratory tract ended. Thus inspired air continues to move toward the alveoli in this order: *Trachea (wind pipe) -> left and right primary bronchi -> secondary bronchi -> tertiary bronchi -> bronchioles -> terminal bronchioles -> respiratory bronchioles -> alveolar duct -> alveolar sac -> alveoli (end of tract)*.

Function of Lower Respiratory Tract

The lower respiratory tract is primarily about conducting air to and from the alveoli, the site of gas exchange. The term alveolus means a 'small cavity', and the alveoli of the lungs are very much like small air cavities. Form the outer surface they resemble a bundles of grapes bunched together. The alveolar duct leads into the alveolar sac providing entrance into the individual alveoli. There are approximately 150 million alveoli in each lung, so the total in both lungs is about 300 million alveoli. The details of the alveoli are discussed in sections ahead. For now it is important to know that the alveolar surfaces represent the exchange structure in the respiratory system, exactly like the capillary is the exchange vessel in the cardiovascular system. In fact, the outer surface of the alveolar sacs are almost completely covered in pulmonary capillaries (see **Figure 18.5**). The gases (O_2 and CO_2) are exchanged between the alveoli and the pulmonary capillary.

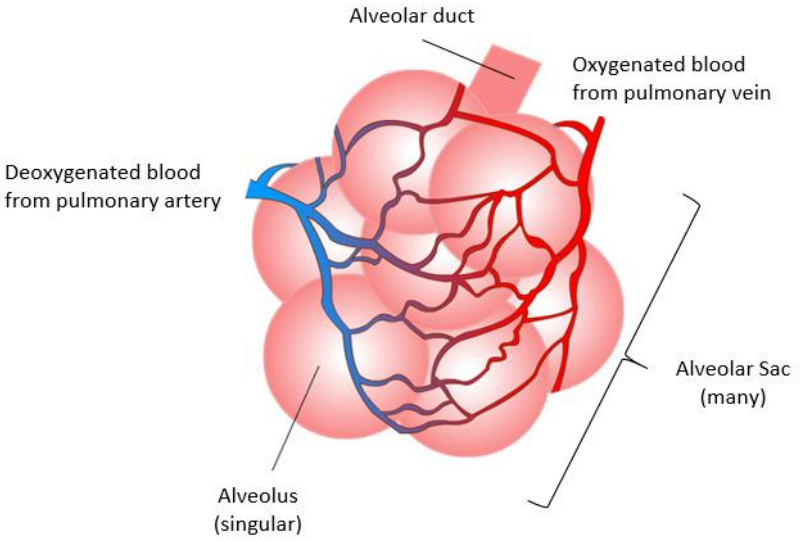


Figure 18.5 Shows the terminal portion of the respiratory tract, ending in the alveolus.

During expiration (breathing out), the air moves out of tract by going back the way it came in. Not all the air in the respiratory tract will make it to the site of gas exchange at the alveoli, and this volume of air is called **anatomic dead space**, because it is air in segments of the respiratory tract that conduct air to the alveoli and respiratory bronchioles but do not take part in the process of gas exchange itself. In a typical adult that volume is about 150 ml of air. This volume is an important difference and plays a role in the calculation of **total pulmonary ventilation** versus **alveolar ventilation** (seen later in chapter).

Zones or Portions of the Respiratory Tract

The respiratory tract can also be divided into two zones or portions. They are: **1)** the conduction zone (or conducting portion); and **2)** the respiratory zone (or respiratory portion).

1) The conduction zone of the respiratory tract consists of the airways that move and deliver air to and from the exchange surface of lungs but is not involved in gas exchange. This zone starts at the **nose** and ends at the **terminal bronchioles**. The 'terminal' in the name denotes an end of a region.

2) The respiratory zone of the respiratory tract is from the **respiratory bronchioles** to the **alveoli** where gas exchange occurs. The lining of the passage way changes from pseudostratified ciliated columnar epithelium to simple cuboidal at the respiratory bronchioles, allowing for gas exchange. It then becomes the thinnest lining of simple squamous at the alveoli to maximize gas exchange in this region.

Respiratory Epithelium

Recall that protection of the body is a function of the respiratory system, and the very tissue lining most of the air passages provide significant protection against anything that does not belong there. With only a few exceptions that we will identify, the entire respiratory tract is lined with **pseudostratified ciliated columnar epithelium**, and it is called **Respiratory Epithelium**.

The respiratory epithelium is part of a mucous membrane so it has a **wet and sticky** exposed surface that is covered in thick viscous **mucus**. The pseudostratified ciliated columnar epithelial layer is technically only one cell layer thick (and therefore is a simple epithelial tissue), however the tall columnar cells and the stem cells below create a formidable physical barrier to the outside environment that is faces. In addition, on the apical (exposed) surface of respiratory epithelium are **cilia,** the hair-like structures that beat rhythmically to create a motion and current that sweeps the mucus upward in what is sometimes called 'the mucus escalator'. Along with the mucus is any debris or particulates that may be stuck in it, taking it up from the lower bronchi and trachea toward the pharynx where it can be ejected.

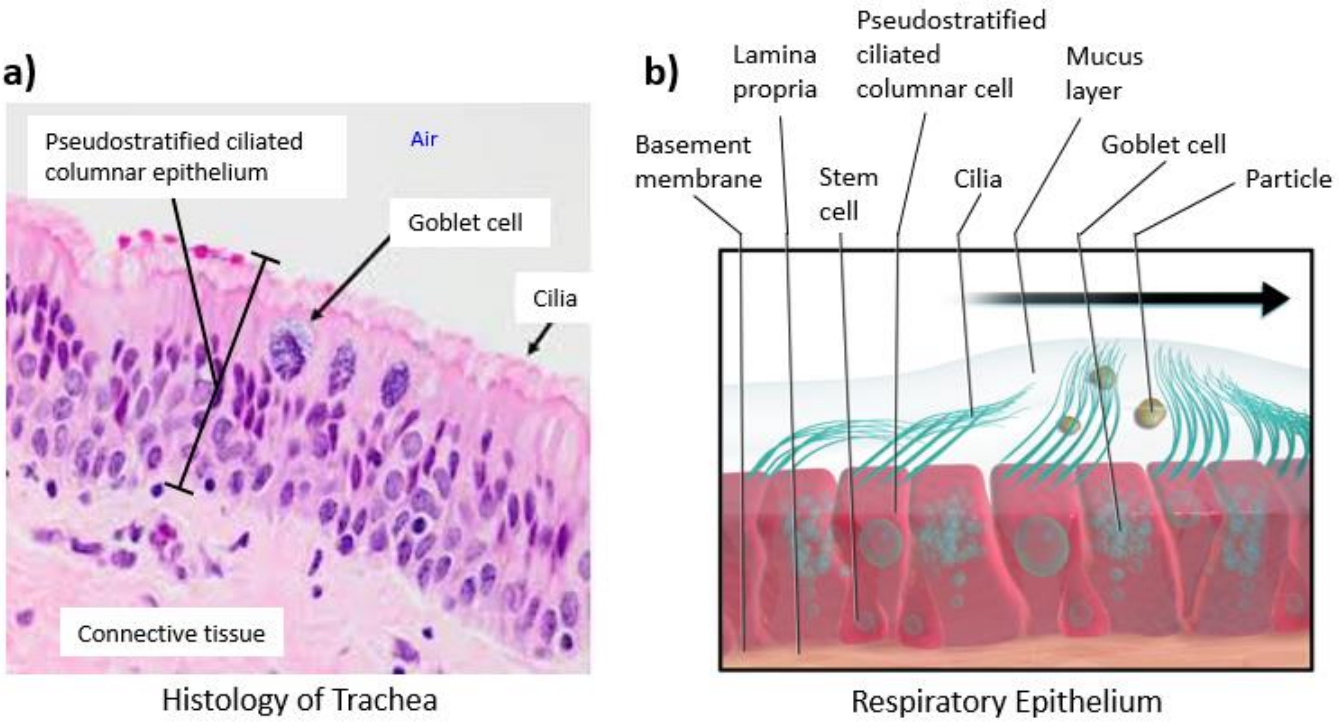


Figure 18.6 Shows **a)** a photograph of the histology of the trachea which is covered in pseudostratified ciliated columnar epithelium. The goblet cells that create the mucus layer and the cilia are also seen. The drawing in **b)** labels all of the components of the respiratory epithelium, with the arrow showing the direction of movement of the mucus.

Disruptions of Respiratory Epithelium

The clearance provided by the **muco-ciliary system** can be impaired by chronic obstructive pulmonary disease (COPD) such as **bronchitis** and **emphysema**, as well as **cystic fibrosis** and **sinusitis**. The hypersecretion of mucus, coupled with a decreased movement of mucus can lead to stagnant mucus that invites bacterial infection. Not to mention this also obstructs air flow. Chronic smoking (of anything) or inhaling any toxic fumes, for example from laundry fragrances or other carcinogens, can also induce abnormal cilia function which can prevent proper clearance of the tract. This often required a person to cough aggressively to try to dislodge and move the stuck mucus out of the tract.

Regions without Respiratory Epithelium

The only regions of the respiratory tract not covered by this protective lining are the following:

a) Two specific portions of the pharynx (throat) called the **oropharynx** and **laryngopharynx**. This is because these surfaces are shared with the digestive track and are covered by the robust **stratified squamous epithelium** that offers protection against the mechanical strass of food ingestion.

b) The **respiratory bronchioles** change into **simple cuboidal epithelium** as they lead into the alveolar ducts. This is a thinner lining that starts to allow for diffusion of gases. This transition is in preparation for the flattest thinnest surface in the lungs at the alveoli.

c) Finally at the **alveoli** the surface exposed to air becomes **simple squamous epithelium** the thinnest lining which allows for the greatest gas exchange.

Pressure Gradients

Just as chemicals naturally and spontaneously move down their concertation gradients, so too does air. Air moves **down its pressure gradient** and breathing air in and out from the environment (**ventilation**) is caused by **changes in the volume of the thoracic cavity**.

The lungs are located in the thoracic cavity and as the volume of the thoracic cavity increases, the pressure inside this cavity (and thus in the lungs) decreases. As the volume of the thoracic cavity decreases, the pressure increases. Therefore, the movement of the thorax creates alternating conditions of high and low pressure within lungs. This creates air exchange in response to **pressure gradients**. Air will always flow **down** its pressure gradient! So wherever the pressure is lower, that is the direction that air will flow.

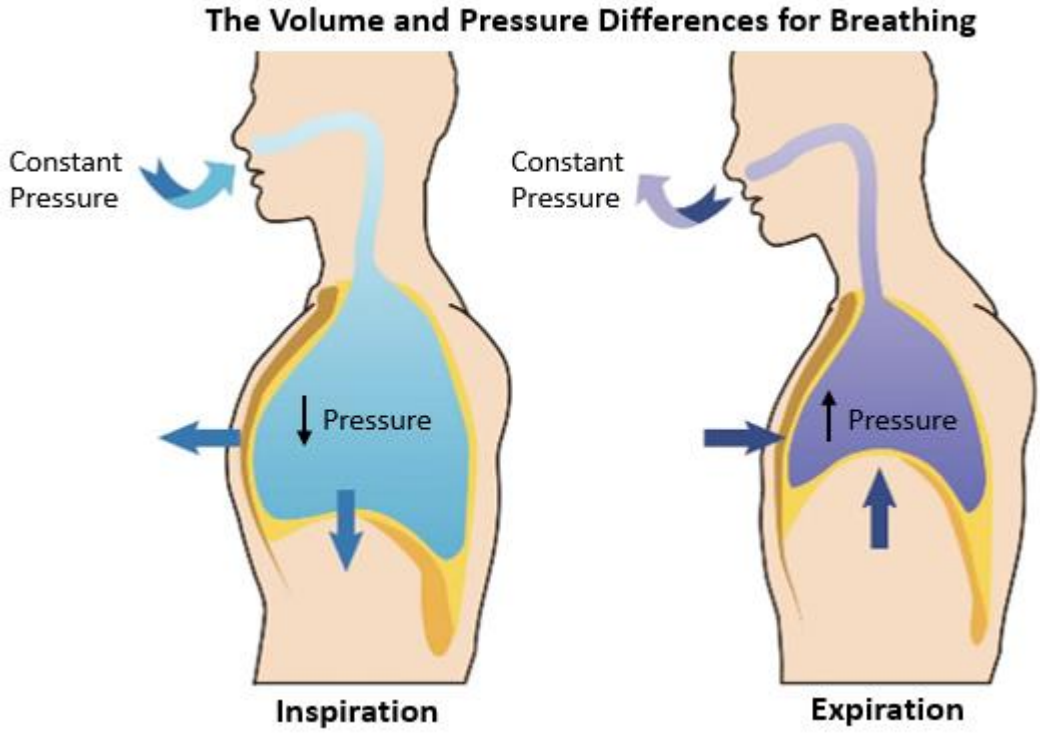


Figure 18.7 This shows how for inspiration (left), the pressure in the thoracic cavity must go down so that air will flow down its pressure gradient into the lungs. For expiration (right) the pressure in the thoracic cavity is increased and air again goes down its gradient to the outside. Since the atmospheric pressure is constant the only changes in pressure occur in the thoracic cavity. The oscillatory changes in pressure there creating breathing in and out.

Thoracic Volume

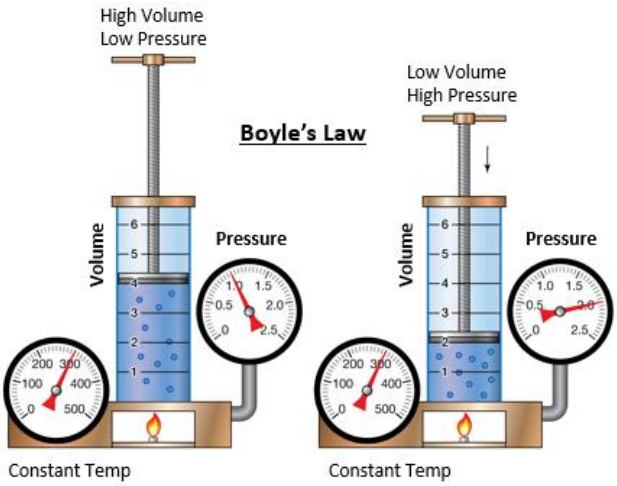
When we see someone's thoracic cavity (chest) expand as they are breathing in, it may initially be thought that the incoming air has inflated their chest. However, that is not what is occurring! What is actually occurring is that the volume of the thoracic cavity (chest) has been enlarged by the contraction of respiratory muscles to expand its volume. So the expansion of the volume occurs before it fills with air. This increase in volume creates a drop in pressure in the thoracic cavity. It is this drop in pressure that causes air to enter the lungs, down its pressure gradient.

Similarly when someone is exhaling, the air leaving the lungs is not what shrinks the cavity. The relaxation of respiratory muscles (during restful breathing or eupnea) or the contraction of expiratory muscles (during forceful breathing) cause the thoracic volume to decrease. This increases the pressure in the thoracic cavity. This increase in pressure that causes air to leave the lungs, down its pressure gradient.

Boyle's Law Describes Pressure-Volume Relationship of Gases

The relationship between the pressure and volume of a gas is described by **Boyle's Law**. The law specifically states that at a fixed temperature, the volume of gas is **inversely proportional** to the pressure of the gas. In other words if one gets larger, the other gets smaller – as we have seen in the thoracic cavity.

Gas pressure in a sealed container is created by the collision of gas molecules with the walls of the container and each other. The smaller the container, the more frequent the collisions, resulting in higher pressures.



The formula for Boyle's Law is: $\mathbf{P_1 V_1 = P_2 V_2}$, where P_1 and P_2 are the pressure changes that correspond to V_1 and V_1 which are the volume changes (see **Figure 18.8**)To reiterate what has been stated previously (in a container like the thoracic cavity), if volume decreases, pressure increases; and if volume increases, pressure decreases. The changes in the volume of chest cavity during ventilation cause pressure gradients, and this is what creates air flow.

Figure 18.8 The volume and pressure apparatus shows how Boyle's Law works. When the temperature is kept constant, the volume of gas is inversely proportional to the pressure of the gas, such that on the left, when the volume is high, the pressure is low. Inversely, on the right, when the volume is low, the pressure is high.

Summary for Lung Volumes and Pressures

Increase chest volume = decrease pressure - air moves in from atmosphere.
Decrease chest volume = increase pressure - air moves out from body.

Think of a squeeze box or an accordion… expanding the volume sucks air in, squeezing it compresses the volume and pushes air out!

In terms of pressure and volume changes:
Inspiration – Air moves from outside into lungs as volume in the thoracic cavity increases (thus, pressure decreases). **Expiration** – Air moves from lungs to outside as volume in the thoracic cavity decreases (thus, pressure increases).

At the risk of being extremely repetitive, we need to firmly know this relationship - that the volume changes create the pressure gradients. It can happen the other way around in that pressure changes can create volume changes, absolutely, but in the lungs the volume changes first, which then instigates the inverse changes in pressure. Succinctly: As volume decreases, pressure increases and vice versa. Changes in the volume of chest cavity during ventilation cause pressure gradients. There. Done.

Ventilation

Ventilation is the movement of air between the environment and the lungs. By now we already know it is changes in volume that precipitate the changes in pressure of the thoracic cavity. At this point the focus will be on the exact and predictable changes in the pressure of specific locations. There are three pressures we need to examine, but for now we need to understand the exact values of two: **Atmospheric Pressure** (P_{ATM}) and **Alveolar Pressure** (P_{ALV}).

Atmospheric Pressure (P_{ATM}) is the weight of the column of air above us. At **Sea Level** it has a value of **760 mmHg** (which is 760 torr or 1 atmosphere).

Alveolar Pressure (P_{ALV}) is the pressure inside the alveoli of the lungs. This pressure needs to oscillate **below** and **above** atmospheric pressure in order to have air flow (down its pressure gradient) into and out of the lungs respectively. See **Figure 18.9** below for the pressure differences of the lung at rest, during inspiration and during expiration.

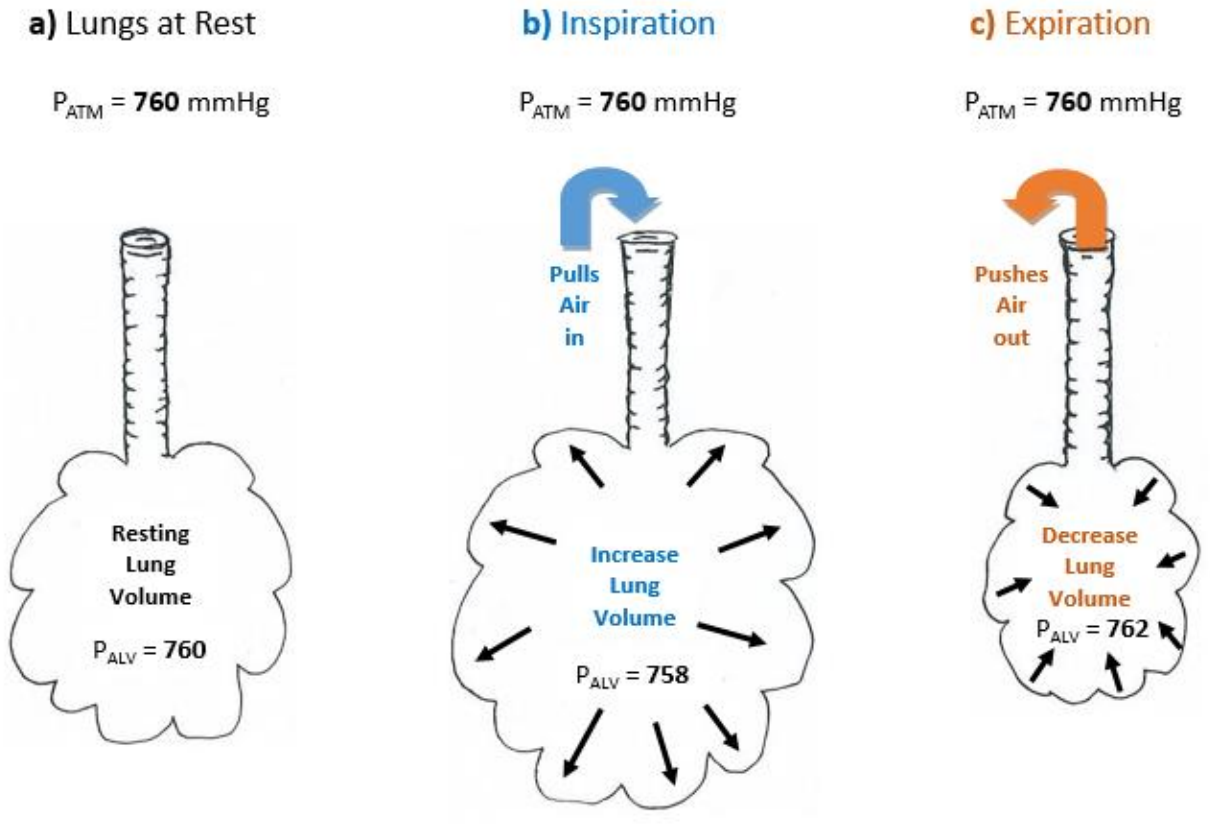


Figure 18.9 At rest **a)** there is no pressure differences between the atmospheric pressure (P_{ATM}) and alveolar pressure (P_{ALV}) so there is no movement of air in or out. During inspiration **b)** lung volume increases and the pressure drops from 760 to 758 mmHg. Now there is a pressure gradient with the P_{ATM} (which remains constant) and air moves into the alveoli down its pressure gradient. During expiration **c)** lung volume decreases, pressure rises to 762mmHg and air moves out of the alveoli into the atmosphere down its pressure gradient.

Make a Set of Lungs

It is actually not too hard to construct a very simplified facsimile of a set of lungs. The diagram below shows how it may be done with a jar, a stopper, some straws, and at about 3 balloons.

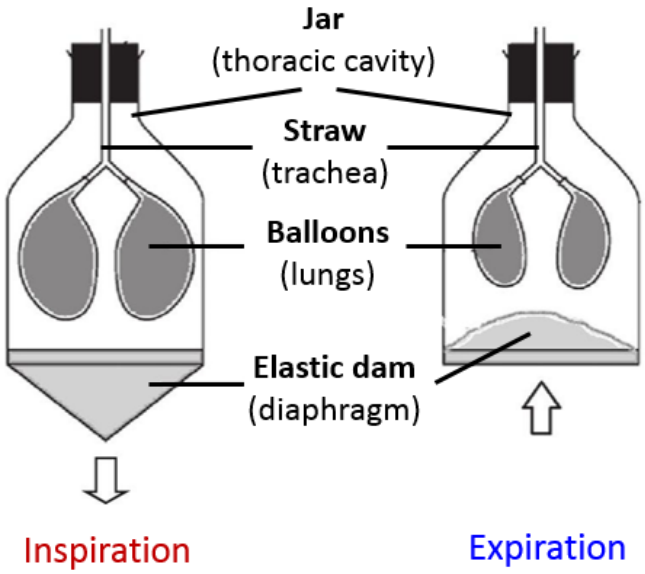


Figure 18.10 Shown above is a simple facsimile to demonstrate the basic structural arrangement of the lungs and how they work. It is constructed with a jar that has an elastic rubber dam secured covering bottom, with a stopper on top that allows a straw through. This enclosed container with one opening is very much like the thoracic cavity. The one straw (the trachea) braches of into two (primary bronchi) and into the two balloons (lungs). The expandable and compassable rubber portion at the bottom (diaphragm) changes the volume of the container, and air moves in and out of the balloons accordingly down its pressure gradient.

Structures and Muscles of the Thorax Surround the Lungs

The thoracic cage is created by the bones and muscles composing the **thorax**. These are the ribs at the sides and front, the spinal column in the back, and the **diaphragm** on the floor of the thoracic cavity. A simplified representation of the inflatable lungs within the thoracic cavity is seen in **Fig. 18.10** above.

Muscle Action of Ventilation

Muscle contraction and relaxation means Action! Muscle get things done! All of the muscles of respiration discussed here are **skeletal muscle** and therefore innervated by the **somatic nervous system**. The somatic motor neurons controlling these muscles of ventilation originate in a network of respiratory neurons in the **medulla oblongata**. It is the medulla oblongata which sets the rhythmic pace of breathing (covered in later sections).

The Diaphragm

The **diaphragm** is the primary muscle of respiration. It is a large dome-shaped **skeletal muscle** forming the base of the thoracic cavity. When it contracts the dome shape compresses and flattens down, thereby enlarging the chest cavity – creating greater volume and therefore lower pressure! Thus, air flows into the lungs down its pressure gradient. When the diaphragm muscle relaxes, the muscle goes back up and pushes into the thoracic cavity and decreases its volume, thereby increasing the pressure and pushes air out. The thoracic cavity is effectively a sealed cavity that contains 3 membranous bags; one around the heart (the **pericardial sac**) and then there is one bag around each lung (the 2 **pleural sacs**).

Muscles Used for Breathing

There are different sets of muscles for inspiration and expiration. Also, different muscles will be employed depending on if the breathing **eupnea**, the term for quiet normal breathing at rest, or if forced breathing is occurring. Below **Fig.18.11** shows the muscles **Inspiration** on the left and **Expiration** on the right.

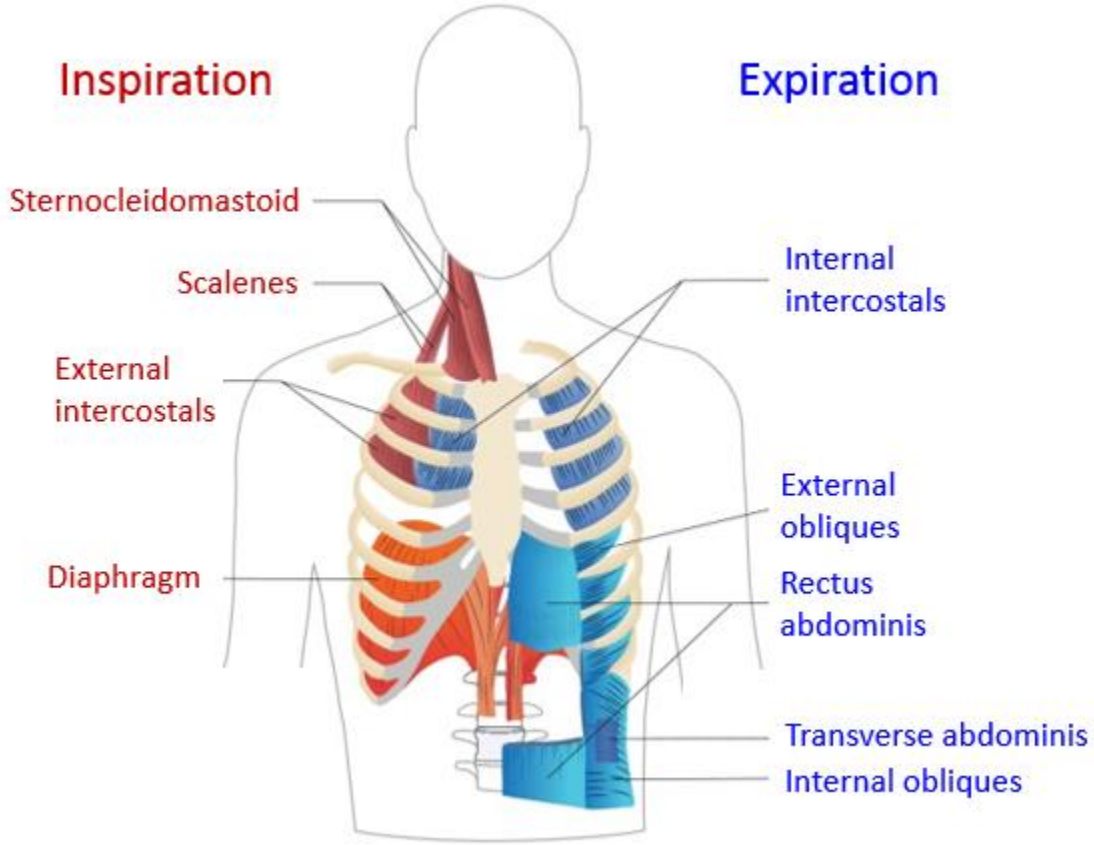


Figure 18.11 The major respiratory muscles are shown with their locations. It also divides their function into muscles of **inspiration** (left) and muscles of **expiration** (right). Note that during eupnea, no expiratory muscles are required, it occurs passively as a consequence of the elasticity of the lung tissue. Expiratory muscles are required only required for forced expiration.

In Eupnea:

A) Inspiration: This requires the contraction of the **Diaphragm** and the **External intercostals**. When the diaphragm contracts, dome-shape collapses, elongating the thoracic into the abdominal cavity. It is controlled by the **phrenic nerve** that arises from the cervical plexus. The external intercostals are the superficial muscles in between the ribs. When they contract they laterally expand the rib cage, like an accordion gets wider when pulled out.

B) Expiration: The pushing of air out of the lungs during eupnea requires **No Muscle Contraction**! The elastic fibers in the lung tissues provide elastance, and when the force stretching the lungs is removed (meaning when the inspiratory muscles relax), the lungs naturally recoil to their original state and by doing so expel air passively. The lungs actually are much like balloons. Think of how much work goes into the inflating them, and by simply letting go of the tip it deflates spontaneously.

Note: The typical metabolic cost of breathing at rest is normally ~ **3%** of Basal Metabolic Rate (BMR). This becomes important when respiratory disorders make breathing more work and become taxing.

In Forceful Breathing:
This occurs for example, during exercise, when breathing is elevated to meet increased metabolic needs.
A) Inspiration: During forced breathing these are the muscles that are used: **Diaphragm**, **External intercostals**, **Sternocleidomastoids** and **Scalenes** muscle. The diaphragm and external intercostals we've seen before during eupnea, the other two muscles are connected to the top of the thoracic cavity and when they contract they add to the lengthening at the top end of the thoracic cavity.

B) Expiration: When forcefully breathing it is necessary to contract skeletal muscle to squeeze the thoracic cavity and push air out more rapidly that occurs form elastic recoil of the lungs. The **Internal intercostals** and the **abdominal** muscles contract to force the air out during forceful breathing. These muscles compress the thoracic cavity and increase the pressure to expel air. There are 4 pairs of abdominal muscles, they are: the **rectus abdominis**, the **transverse abdominis**, the **internal obliques** and the **external obliques**. Compression of these act to further compress the thoracic cavity above. If you blow out candles with a forceful breath, you can feel your abdominal muscle contracting to generate that force.

The Lungs are enclosed in Pleural Sacs
The lungs are a light, spongy tissue mostly occupied by air-filled spaces (the millions of alveoli). Due to the positioning of the heart slightly to the left in the thoracic cavity, the left lung has the 'cardiac notch' which is occupied by the heart, making the left lung a bit smaller than the right. Each lung is contained in double-walled **pleural sac** and on its inner surface is a serous membrane called the **parietal pleura**. The outermost surface of the lungs is also a serous membrane called the **visceral pleura** (see **Fig. 18.12** at right). The naming pattern and the function of this arrangement are identical to the pericardial sac around the heart. Its role is to reduce friction between the two surfaces that are constantly moving across one another during each breath as the lungs expand and contract.

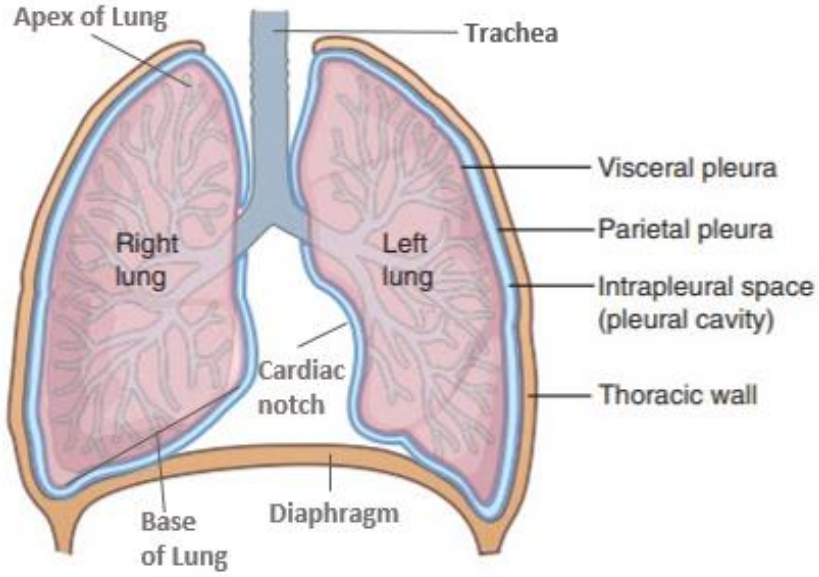
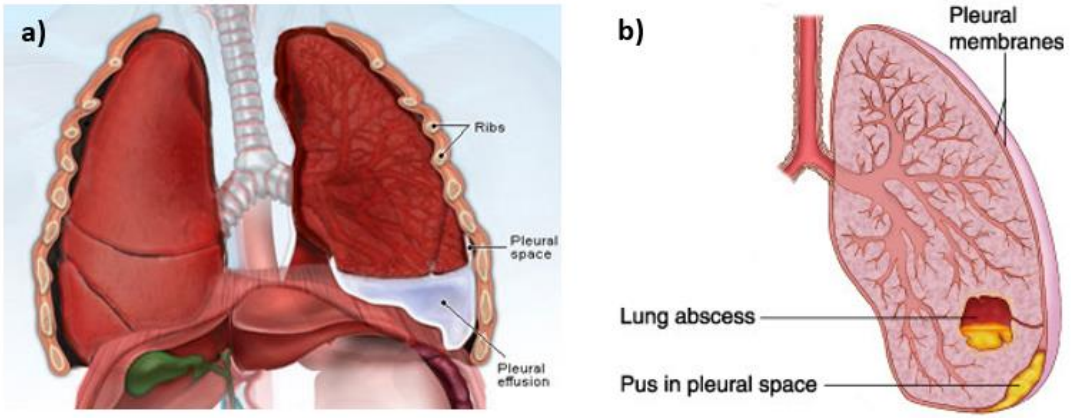


Figure 18.12 The two lungs are shown with the apex at the top and the broad base of the lungs at the bottom. Each lung is protected by its own pleural sac that contains a slippery fluid filled pleural cavity.

The narrow apex of each lung is at the top of the thoracic cavity, under the upper ribs and the clavicle. From the upper respiratory tract, it is the trachea (wind pipe) that connects the lungs to the atmosphere. The trachea divides into two primary bronchi, the left and right, which go into the two lungs. These lungs are divided into lobes: The right lung has three lobes, and the left lung has two lobes (*tri before you bi*).

The lungs are like an air-filled balloon surrounded by a water-filled balloon. Inside the plural cavity sits the **pleural fluid**, which holds opposing the pleural layers together, creating a slippery surface allowing movement of the membranes as the lungs move to reduce friction. The fluid filled plural cavity also holds

the lungs tight and in a stretched state against thoracic wall due to fluid's cohesiveness. This becomes an important aspect to remember.



Pleural Effusion – excess pleural fluid

Empyema - pus in pleural cavity

Figure 18.13 Disruptions of the plural membranes are show in **a)** plural effusion when too much plural fluid accumulates and can hamper expansion of the lungs. Also seen is **b)** empyema (not emphysema!) which is when pus accumulates in the plural cavity, in addition to a lung abscess, in which lung tissue is filled with pus.

The Alveoli are the Site of Gas Exchange

An alveolus (singular) is the structure where gas exchange occurs in the lungs.. An alveolus is mostly composed of simple squamous epithelium. That is, it's made of a single cell layer of thin, flat epithelium that creates the walls for gas exchange. It also has two others cells present, that although not as numerous at the epithelial cells, play a vital role in the functioning and protection of the lungs.

There are 3 types of cells in Alveoli

1. Type I Alveolar Cells: These are simple squamous epithelial cells. They are the most abundant of the cell types in the alveoli. They are very flat and thin to maximize gas exchange between the alveoli and the pulmonary capillaries. From the very early sections on diffusion, we know that the thinner the barrier the faster the rate of exchange. We also know that the greater the surface area the greater the rate of exchange, and the lungs have that covered as well. Since there are about 300 million alveoli in the lungs that creates an enormous areas for gas exchange to occur on.

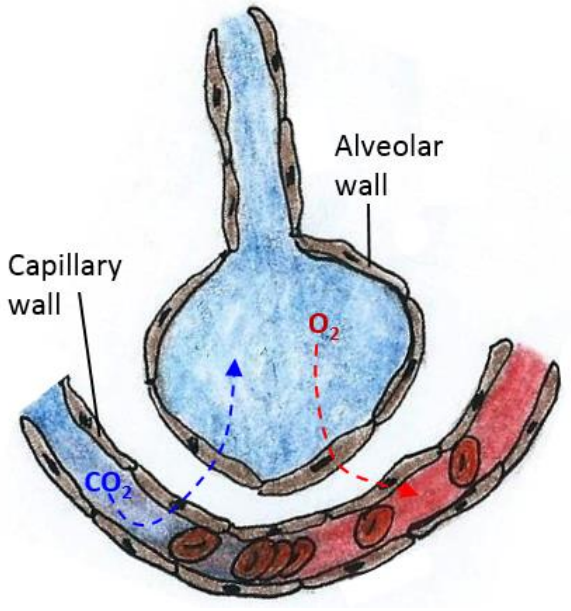


Figure 18.14 The close arrangement of the air filled alveolus and the diffusions of gases with the pulmonary capillaries that surround it.

There is a continuous diffusion of oxygen (O_2) from the alveoli into the pulmonary capillaries, and of carbon dioxide (CO_2) from the pulmonary capillaries into the alveoli (see **Figure 18.14** at left). Aside from creating the walls for gas exchange, these type I alveolar cells also release a molecule called **α anti-trypsin**. This substance is like a waxy coating for their inner surface and it protects them against the digestive enzyme **trypsin** that is normally released by **alveolar macrophages**.

2. Type II Alveolar Cells: These are also called 'septal' cells because they are often found in the septum (divider) between the alveoli. They are far less abundant than type I cells. They are thicker cells which make and secrete pulmonary **surfactant**.

At this point it is worth noting that the inner surface of all alveoli are **covered with water**, this is absolutely necessary for gas exchange to occur. Surfactant is a phospho-lipo-protein molecule that is soluble in both water and lipids (**amphiphilic**). When surfactant molecules are released from type alveolar II cells, they sit on the wet inner surface of the alveoli directly in between the water molecules. Since water has a very high affinity for itself, water usually generates significant **surface tension** on the inner alveoli. Left unchecked, this surface tension has a tendency to cause alveoli to collapse too far. The surfactant, by sitting in between the water (H_2O) molecules on the inner surface, acts to reduce the surface tension generated by the high affinity H_2O has for itself. This prevents significant collapsing of alveoli, which allows the alveoli to re-expand with ease, and yet still maintain elastic recoil necessary for passive exhaling.

3. Alveolar Macrophages: These are macrophages that reside in the lung tissue, and like all other macrophages they are derived from monocytes (WBC) and they **phagocytose** any foreign particles that might make it down to the alveoli. Thus, they protect and defend the lung tissue. If they encounter an inhaled irritant, they release **trypsin**, a powerful digestive enzyme that degrades proteins.

Capillaries cover 80-90% of the alveolar surface forming an almost continuous blood-air contact. **Gas exchange occurs by simple diffusion**. The single endothelial cell of the capillary and the single squamous epithelium of the alveoli have a fused basement membrane in between them, this arrangement allows for a rapid diffusion of gases.

Note: The alveoli do not contain muscle fibers and cannot contract independently by themselves. They can however expand and contract in a measured way, and this is due to the **elastic fibers** that are in between and surround the outside of every alveoli. The elastic nature of the lung tissue is critical to its function and contributes to elastic recoil after the lung tissue is stretched. Diseases like **emphysema** that destroys elastic fibers can have a devastating effect on the normal elastic recoil of the lungs.

The Pulmonary Circulation is a High-Flow, Low-Pressure System

At rest, the **pulmonary circulation** of the cardiovascular system contains about 0.5 L of blood (that is about 10% of total blood volume) with 75 ml in the capillaries for gas exchange. Remember that when we are at rest, most of our blood is diligently moving along in the systemic veins.

It turns out, the rate of blood flow through the lungs is greater than that of other tissues, which makes sense because gas exchange in the lungs is paramount. Consider that the lungs receive the entire volume of the right ventricle cardiac output, which at rest is about 5 L/min. That is the same volume that the rest of the body receives via the left ventricle cardiac output (5 L/min). The difference is that the pulmonary circulation has very low pressure, with an average pressure = 25/8 mm Hg compared to 120/80 mm Hg in systemic blood pressure. This correlates with low pulmonary resistance; in other words, the higher flow rate in the lungs is achieved in part due to the lower pressure, together with the vast capillary beds and larger blood vessels.

Differences between the Pulmonary and Systemic Systems

The pulmonary arteries are much more **compliant** (distensible, easier to stretch) than the aorta and other systemic arteries. Also, the total length of pulmonary blood vessels is shorter. As we have already discussed, this means that the right ventricle doesn't have to pump as hard to overcome peripheral resistance.

As seen in the cardiovascular sections, this is the very reason that allows for low pulmonary blood pressure to exist. An important consequence of this low blood pressure means there is a net **low hydrostatic pressure**, thus yielding low fluid flow into the interstitial spaces. As we have seen, the lymphatic system removes excess filtered fluid from the tissue spaces, and in the lungs, there is a *much smaller volume of interstitial fluid* generated from the pulmonary capillaries (less than 0.5 L/day) compared to the loss of 3 L/day from the systemic capillaries. This is one reason why **pulmonary edema** is so detrimental, as increases in the interstitial fluid volume can greatly hamper gas exchange. This and other conditions that hamper gas exchange will be discussed in later sections.

GAS LAWS - Air is a Mixture of Gases

The atmosphere contains a mixture of gases and water vapor. The main components of the air we breathe in is Nitrogen gas (N_2) and Oxygen gas (O_2). There is also H_2O in vapor form (which is defined as the humidity of the air) and a very low level of CO_2 in the atmosphere as well. There are also inert gases such as argon, ozone, sulfur dioxide, and carbon monoxide, and pollutants present in air in varying trace amounts.

Since the air we inhale is a mixture of gases, we will need to know about the partial pressure of a gas in order to determine how one gas in a mixture of gases will move (diffuse) in the body. **Partial pressure** is the pressure exerted by an individual gas in a mixture of gases, if it alone occupied the entire volume occupied by the mixture of gases. Just like pressure gradients, there are also partial pressure gradients in the body, and knowing the partial pressures of O_2 and CO_2 will indicate which direction they will travel when they move down their partial pressure gradients.

Dalton's Law

The total pressure of a gaseous mixture is the sum of individual gas (partial) pressures (see image below in **Figure 18.15**). **Individual gases move down their partial pressure gradients**. It is **Dalton's Law** that describes the total pressure of a mixture of gases is equal to the sum of all of the partial pressures of the individual component gases. The way that gas exchange occurs in the body is that an *individual* gas in that mixture of gases moves from areas of *higher partial pressure* for that gas to areas of *lower partial pressure* for that single gas. We will focus on levels for O_2 and CO_2.

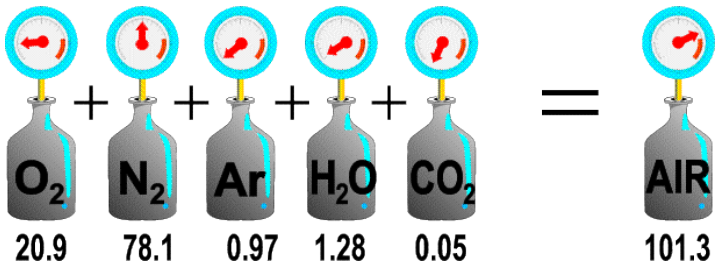


Figure 18.15 Air is a mixture of gases, and the total pressure of air is the sum of individual gas (partial) pressures. Here the pressure values are given as kilo pascals (kPa), where 101.3 kPa is approximately 1 atmosphere (ATM) which is equivalent to 760 mmHg.

Partial Pressures = P_{ATM} x % of gas in atmosphere. Partial pressures vary with amount of water vapor.

Air is a mixture of gases. **N_2 = 79%**
O_2 = 21%
CO_2 = 0.03%

If atmospheric pressure of air at sea level is 760 mmHg (a standard value) and air is a mixture of the above gases (N_2, O_2 and CO_2), then we can calculate the *partial pressure* exerted by each gas in this mixture of gases. The partial pressure of N_2 is symbolized by P_{N2} and partial pressure of O_2 is P_{O2}, etc.

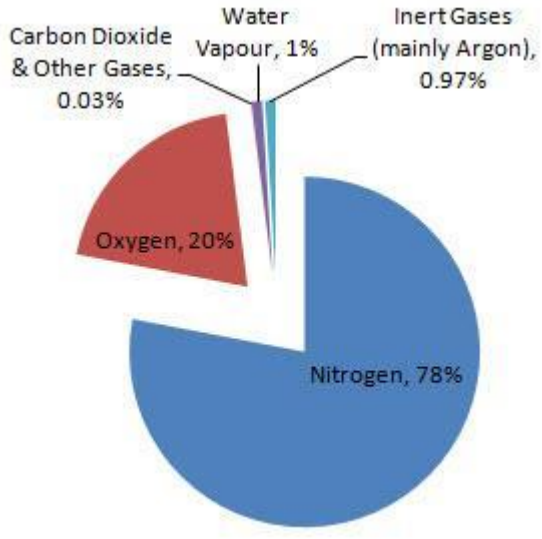


Figure 18.16 The pie chart above shows the percentages (%) of the various gases, such as nitrogen, oxygen, water vapor (gas) and other inert geese that make up the components of the air we breathe.

Calculating Partial Pressures of gases in air at sea level

1) **P_{N2}** = P_{ATM} x % of gas in mixture (79%, = **0.79**)

= **760** mm Hg x **0.79**

= **600** mm Hg

2) **P_{O2}** = P_{ATM} x % of gas in mixture (21%, = **0.21**)

= 760 mm Hg x 0.21

= **160 mm Hg**

3) **P_{CO2}** = P_{ATM} x % of gas in mixture (0.03%, = **0.003**)

= 760 mm Hg x 0.003

= **0.24 mm Hg** (which is negligible)

Thus, at sea level, the partial pressure of oxygen (P_{O2}) is about 160 mmHg. This can be thought of as the amount of O_2 that is available to be extracted from the environment by the lungs.

As we will see later, the actual partial pressure of oxygen (P_{O2}) that makes it down to the alveoli is less than this amount available in the atmosphere, for various reasons we will examine.

Gas Solubility in a Liquid

The Solubility of a Gas in a Liquid Depends on Pressure, Temperature and Solubility

Where air and water meet, any particular gas will flow from the medium with higher partial pressure to medium with lower partial pressure. Movement of a gas into a liquid is directly proportional to **3** factors:

1. Partial Pressure Gradient of that gas.
The greater the partial pressure gradient, the grater the force pushing that particular gas into a solution and the more soluble the gas is in that liquid. In physiology, the liquid is plasma (which is 92% water).

2. Temperature of the Liquid and surroundings.
The warmer the liquid, the *less soluble* the gas is in it; contrary wise, the colder the liquid, the greater the solubility of the gas in it! This may seem counter intuitive at first. However, think of two open soda cans as an example; one in the fridge and one on the counter. Which one would go flat faster? The soda that sits on the counter becomes warmer than the one in the fridge, and as any solution gets warmer it lets more of the gas dissolved in it escape faster. Colder solutions keep more gases dissolved in them.

3. Solubility of the Gas in that liquid.
Gases have different solubilities in various liquids depending on their molecular **chemistry**. The more soluble a gas is, the less partial pressure that is needed to force the gas into solution. Thus a gas with poorer solubility requires higher partial pressures to move even small amounts of gas into solution.

Oxygen (O_2) is about **20** times less soluble in water than carbon dioxide (CO_2).

This is why there is such a large partial pressure gradient for O_2 (60 mm Hg) compared to the more soluble CO_2 (6 mm Hg). Gases move between phases (i.e., in and out of solution) until **equilibrium** is reached. The partial pressure for a gas in the air phase at equilibrium = Partial Pressure of that gas in liquid phase. However, this does not mean that concentrations are equal! The concentrations depend on the **solubility** of the very molecules, all of which are unique. Since O_2 is far less soluble (chemically) than CO_2 in plasma, this explains why O_2 needs oxygen-carrying compounds in blood, such as hemoglobin (Hb), in order to capture more of the dissolved O_2 and transport it around the body.

Like Blood Flow, Air Flow during Ventilation is related to the Pressure Gradient and Airway Resistance

As previously discussed, the lungs are held to the thoracic cage by pleural fluid and contraction of thoracic muscles creates the changing volumes, which generate the pressure gradients. Air flow in the respiratory system obeys the same rules as blood flow inside of vessels. The driving force for air flow is the pressure gradient and resistance opposes air flow. We can use the exact same formula (below) and make the observation that flow increases as the pressure gradient (ΔP) increases, and decreases as resistance (R) increases.

$$\text{Air Flow} = \Delta P/R.$$

Airway Diameter is the Primary Determinant of Airway Resistance

Again, like blood flow through blood vessels, any resistance (R) to air flow in the respiratory tract must be overcome by the **ΔP**, for air to flow (related to work of breathing). If there is more R to air flow, then more energy must be expended to overcome that resistance, meaning there is a need to breathe more forcefully. The same influences that define **Poiseuille's Law** for blood flow are at work here: Length (L),

viscosity (η), and radius (r) all have an impact on resistance (R). The length of air pipes and viscosity of air are essentially constant in respiratory system (as was the case in the cardiovascular system for blood). Also like blood vessels, it is the radius of the airways that become a primary determinant of resistance to air flow. About 90% of airway resistance is due to the trachea and bronchi, but the cartilage maintains a constant diameter, and prevents these air pipes from closing down significantly.

Control of Airway Resistance

The **bronchioles** in the respiratory tract are the structures that can most significantly adjust their diameter and therefore alter resistance to air flow. The bronchioles do not have any cartilage but do have smooth muscle, this allows them to change diameter and significantly regulate air flow in the lungs.

Bronchoconstriction – this is the term used to describe **constriction** of bronchioles.
Bronchoconstriction increases the resistance to air flow and decreases the amount of fresh air to alveoli. These changes are under nervous, hormonal, and paracrine control.

1) The **Parasympathetic** division of the ANS causes bronchoconstriction when there is no need for additional air flow ('rest and digest').

2) If **Histamine** is released from tissue mast cells or from basophils this causes bronchoconstriction and a decreased air flow.

3) On a more local and paracrine level, the same response of bronchoconstriction is achieved if there is a **decrease in CO_2** of the surrounding tissue, this indicates that metabolically there is no additional need for more air.

Bronchodilation – this is the term used to describe the **dilation** of bronchioles.
Bronchodilation decreases the resistance to flow and increases the amount of fresh air to alveoli.

1) Stimulation of the **Sympathetic** division of the ANS causes bronchodilation, during the 'fight or flight' response, this is because more air and O_2 are needed by the body.

2) Similarly, if **Epinephrine** (E) is released by the adrenal medulla, this hormone causes bronchodilation (via β2 receptors!) to enhance air flow. This potent dilation of airways by epinephrine is why those who have allergies carry an "EpiPen" around with them in case they encounter an allergen. Injected intramuscularly (IM) the E acts quickly to dilate airways.

3) If there is an **increase in CO_2**, this leads to bronchodilation and an increased air flow, as the elevated CO_2 is indicative of increased metabolic activity and a greater need for O_2.

Exact Pressures for Ventilation in the Respiratory System

1. Atmospheric Pressure (P_{ATM}): This is the weight of the column of air above you. This remains relatively constant however, when changing altitude can change dramatically. At sea level this value is **760** mmHg. At higher altitudes the atmospheric pressure become lower because there are fewer molecules above you, therefore less force or pressure from the atmosphere. At low altitudes (below sea level), the weight of the column of air above is greater, therefore the pressure is greater. As we know, the pressure in the lungs must be higher or lower than atmospheric pressure for air flow to be created.

2. Alveolar Pressure (P_{ALV}): This is the pressure inside the alveoli, where gas is exchanged. This pressure normally oscillates between **758** mmHg (inspiration) to **762** mmHg (expiration).

3. (Intra) Pleural Pressure (P_{PLU}): This is the pressure inside the fluid-filled pleural cavity. This pressure is always less than atmospheric and alveolar pressures and normally oscillates between **754** mmHg (inspiration) to **758** mmHg (expiration). It is critical that the pressure in this fluid-filled pleural cavity is **always lower** that the other two pressures in the lung, because this is what keeps the lungs stretched and prevents the lungs from collapsing too far during.

The two lungs (left and right) are each contained within a separate **pleural sac**, encompassing the lung tissue in **the fluid filled pleural cavity**. The outermost lining of the lungs is the visceral pleura, and the inner lining of the sac is the parietal pleura, together creating a serous membrane. There is a thin film of serous fluid between with two linings, which reduces friction between the two surfaces when the lungs continually expand and contract.

Transmural Pressure Gradient

The fact that the pressure in the pleural cavity is always kept lower than the pressure in the alveoli ensures that the lungs are always in a stretched state, even when compressing to breath out. The air in the alveoli that has a higher pressure than the fluid in pleural cavity exerts a force across the wall of the lung tissue, as the high pressure air (in alveoli) wants to go where the pressure is lower (in pleural cavity). This force across the lung wall is called the **transmural pressure gradient** (trans = across, mural = wall) and is a force that opposes (or balances) the force of elasticity within the lungs that would cause the lung to collapse. Note in **Figure 18.17** the blue arrow and blue region in the diagram indicates this transmural force.

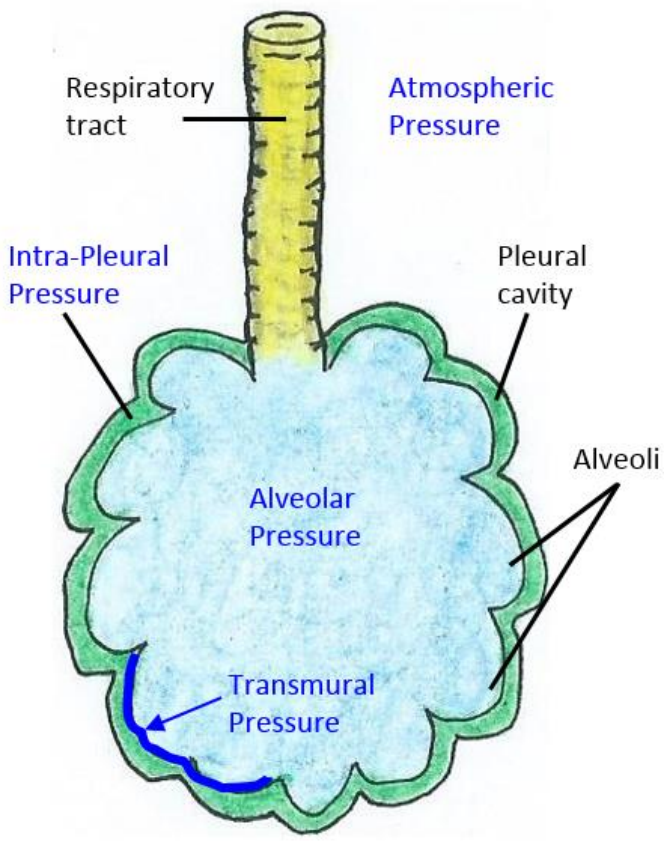


Figure 18.17 The drawing above shows a representation of the respiratory tract and the alveoli. The three pressures, atmospheric, inrta-pleural and alveolar pressure can all be located and also shown is the critical transmural pressure gradient that exist across the alveolar wall.

Inspiration Occurs When Alveolar Pressure Decreases

As mentioned previously, when the thoracic cavity volume increases, pressure decreases and air moves into lungs. Typically, very small changes in alveolar pressure are required for ventilation. When thoracic cavity volume increase, inter-alveolar pressure drops about **2 mmHg** below atmospheric (to about 758 mmHg) and air begins to flow into alveoli. Air flow continues until pressure inside lungs equals atmospheric pressure (760 mmHg). At the end of inspiration, the somatic motor neurons innervating the diaphragm and external intercostals stop firing, causing relaxation. This allows for passive expiration, due to elastic recoil of lungs (this is not due to muscle contraction). Expiration occurs when intra-alveolar pressure exceeds atmospheric pressure (reaches about 762 mmHg).

Active expiration happens during exercise or forced heavy breathing. This occurs during voluntary exhalations and when ventilation exceeds **30-40 breaths/min**. This uses internal intercostals and abdominal muscles (expiratory muscles). Diseases or adverse conditions that afflict skeletal muscle can adversely affect ventilation. Since, as we have seen, there are many skeletal muscles involved in breathing in and out, any significant decrease in contractility of skeletal muscle can hamper both body movement and breathing.

Intrapleural Pressure Changes during Ventilation

The pressure in the **pleural cavity** can be thought of as shadowing the pressure changes in the alveoli, this is in order to always remain lower than alveolar pressure and ensure that the lungs remains stretched! In fact, the intra-pleural pressure is both sub-intra-alveolar and sub-atmospheric (typically ranging from 754 to 758 mm Hg).

Spontaneous and Traumatic Pneumothoraxes

Disrupting the transmural pressure that exists across the walls of the lung can cause a **pneumothorax** – also known as a 'collapsed' lung. This can arise spontaneously (which is not like the 'fun' and spontaneous) through disease which impairs the tissues, most commonly damage to the alveolar tissue. This can also occur from physical trauma impact that could lacerate lung tissue, or if your lungs are punctured by a sharp object, like a knife fight.

Anyway it occurs (puncturing or disruption of the pleural cavity), the end result is that it will compromise the pleural cavity (either internally or externally) which results in the normally sub-alveolar and sub-atmospheric pleural cavity pressure ***equilibrating*** with the other higher pressures. That is bad! As a consequence, the driving force for the transmural pressure gradient that keeps the lungs in their stretched state is removed, and the afflicted lung will collapse under its own elastic recoil (see **Figure 18.18**).

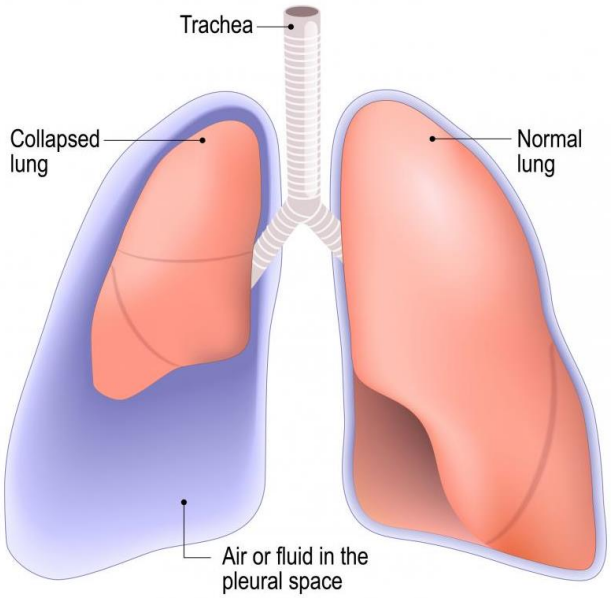


Figure 18.18 A collapsed lung, or pneumothorax, results when the intrapleural pressure equilibrates with the atmospheric and alveolar pressures. This removes the transmural pressure that keeps the lungs stretched, leaving the lung to shrink (as in the right lung). Since each lung has its own separate pleural sac, pneumothorax in one lung will not impact the other lung.

The two lungs are independently sealed in their own pleural cavities such that compromising the pleural cavity of one lung will not necessarily impact the other. Air must be removed from the intra-pleural space and the puncture sealed in order to correct the pneumothorax.

Lung Compliance and Elastance

Pulmonary compliance and elastance are qualities and properties of the lung that may change in disease states. Lung **compliance** is related to the ability of the lungs to stretch and lung **elastance** (or **elasticity**) is the ability of the lungs to recoil after the force stretching them is released.

Lung **compliance** is the ease with which the lungs are able to be stretched. More technically, pulmonary compliance is the amount of work required to stretch (inflate) the lungs. High-compliance lungs are easily stretched, that is, they do not take a lot of energy to inflate. Low-compliance lungs require more force to stretch the lungs, which is more work, which means more energy is required.

High lung compliance doesn't necessarily mean high elastance. In addition, high lung compliance in and of itself is not necessarily a beneficial quality. For example, often with **emphysema** there appears to be a high compliance (a pliable lung), but this is a factor caused by low elastance (elastic recoil).

Low lung compliance is most clearly illustrated with **stiff lung**, as seen commonly in **pulmonary fibrosis**. In this case there may be high elastic recoil but because of the thickening of the type I alveolar cells this disease state requires a lot of energy to expand the lungs, like trying to blow up a stiff thick balloon.

Pulmonary Elasticity vs. Compliance

Pulmonary Elastance = Elasticity. This is about the lungs ability to recoil to its original (un-stretched) state. To recap, **elasticity** (elastance, elastic recoil) means that a structure is able to return to its original shape after the force stretching it has been removed. **Compliance** simply means that a structure can be easily stretched. In physiology, the normal healthy lung has both elastance and compliance.

In lung physiology there is a balance between elasticity and compliance. Below is a summary of how pulmonary elasticity and pulmonary compliance are generated, and how these two forces are finely balanced for optimal lung performance.

Pulmonary Elasticity is generated by 2 elements:

1) Elastic Fibers

These fibers are an integral part of lung tissue. Elastic fibers cover a considerable portion of each alveoli on its outer surface. The natural tendency of these fibers is to recoil after the force stretching them is removed. Importantly, the elastic properties of lung tissue facilitates passive expiration that occurs as a consequence of elastic recoil.

2) Surface Tension

The inner alveolar surface has a thin layer of water on it. The water molecules are absolutely necessary for gas exchange to occur. These water molecules create **surface tension** between the air-fluid boundaries in the alveoli. Surface tension arises due to the strong attractive force that water has for itself. Remember from the beginning of semester, one of the key properties of water is ***cohesion*** (water is said to have a high affinity for itself). The polarity of the water molecule means that it can form hydrogen bonds with itself, creating a cohesive layer of water, generating tension on the surface of the alveoli. This surface

tension generated by water tends to make the round-shaped alveoli collapse inward, because the smaller the alveoli becomes, the closer the water can be to itself; this then creates more cohesion! This is the chemical nature of water. This property of water assist in elastic recoil because it is a force that tends to collapse alveoli. However, it also increases the work needed to stretch the air-filled lung. In this way the force must be balanced. It is useful to have passive recoil, but not useful if it requires far too much energy to re-inflate the alveoli that have collapsed too far.

The role of Surfactant

Simply put, surfactant decreases the work of breathing. The type II alveolar cells make and release pulmonary **surfactant** onto the internal aspect of the alveoli. As mentioned in previous sections, surfactant is a phospho-lipo-protein and it is positioned between the water molecules on the inner surface of the alveoli, reducing the affinity that water has for itself, thus acting to reduce the surface tension generated by water. This creates more compliant lungs, as it required less energy to inflate lungs that have adequate levels of surfactant. This allows the lungs to still exhibit elastic recoil but prevents significant collapsing of alveoli, in addition it also allows the alveoli to expand with ease.

There is also an important stabilizing effect of surfactant on lung tissue because it protects and **maintains the variation in alveoli size**. As described below, the smaller alveoli would collapse into the larger alveoli if it were not for the larger amounts of surfactant in smaller alveoli (see **Figure 18.19**).

Law of La Place

The law of La Place describes the force (pressure) that is created by a fluid sphere or bubble. The pressure (P) depends on surface tension (T) and radius (r). **La Place's Law:** $P = 2T/r$

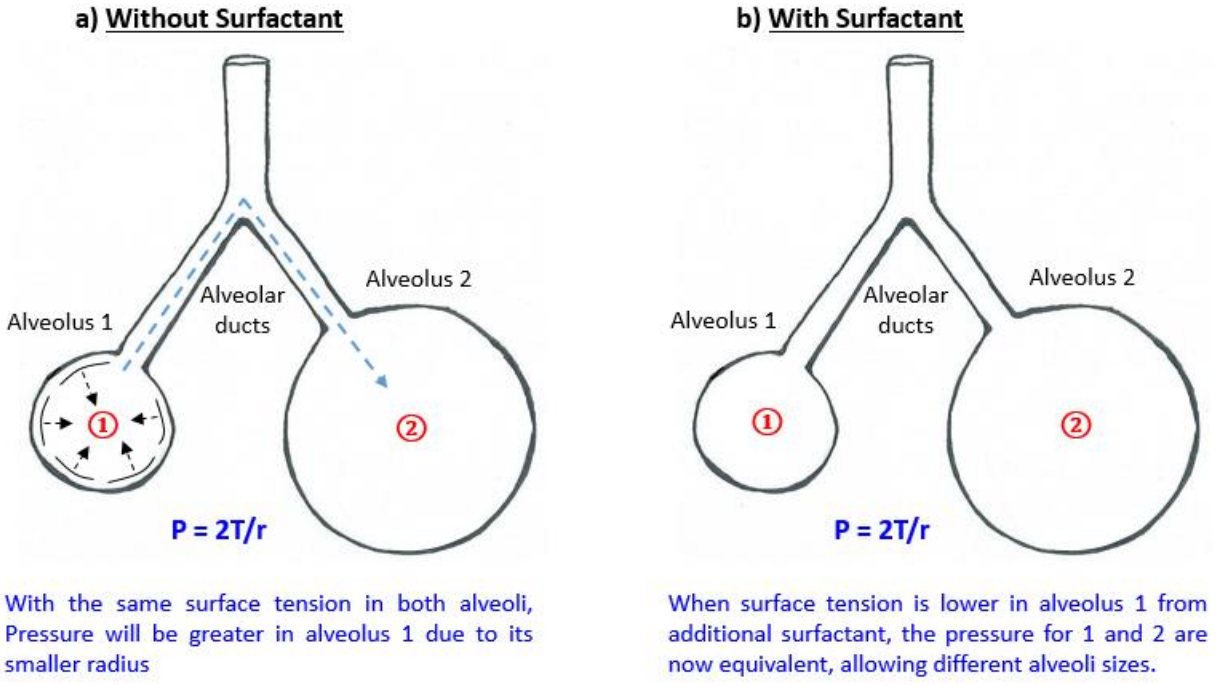


Figure 18.19 In **a)** if the alveoli in a lung were without surfactant, the pressure in a smaller alveolus is higher than that of a larger alveolus, because pressure (P) is calculated as 2 times the surface tension (T), divided by the radius (r). This would cause the air in alveolus 1 to go down its pressure gradient into the larger alveolus 2, seen in **a)**. However, in **b)** if the smaller alveolus has more surfactant than the larger alveolus, the pressure becomes equivalent in both alveoli, preventing the smaller alveoli from collapsing into the larger ones. In this way, surfactant helps stabilizes the alveoli of the lungs, allowing it to maintain its great surface area.

Alveoli are analogous to spheres and behave much like balloons. If two alveoli have different diameters (radii) but are lined with fluids having the same surface tension, according to La Place's law, the pressure inside the smaller alveolus will be greater. This would force the smaller alveoli to collapse into the larger ones. If this were to happen, much of the convoluted surface area of the alveoli would be lost, and this decreases surface area for gas exchange.

The pulmonary **surfactants** reduce surface tension and prevent all alveoli from collapsing into one big 'mega-alveoli'. That would not maintain the enormous surface area that we need for effective gas exchange. Surfactant is more concentrated in smaller alveoli, making its surface tension less than in the larger alveoli. This acts to equalize the pressures among the different sized alveoli. It is useful to think of alveoli as balloons, and **Figure 18.20** below is a very effective and easy demonstration to show anyone how La Place's Law works, and reiterates the need for greater amounts of surfactant in smaller alveoli.

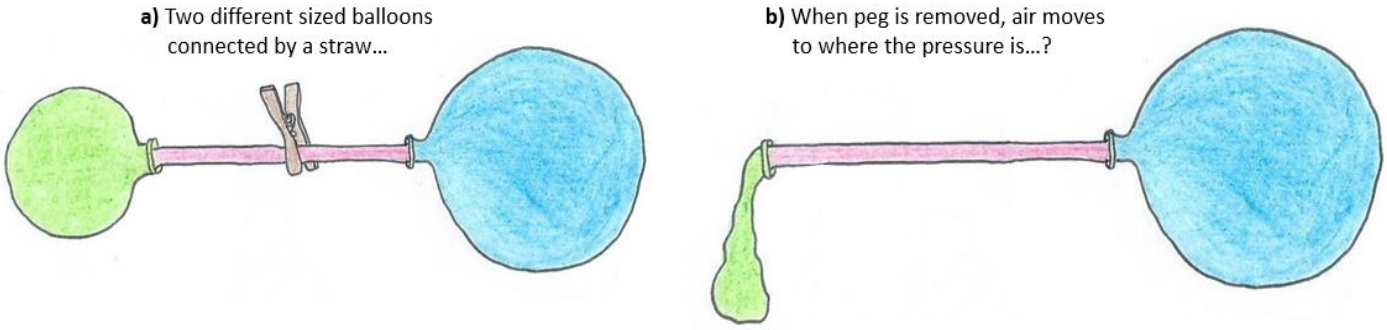


Figure 18.20 A useful and easy experiment to conduct is shown above. Inflate two balloons to different sizes and connect them with a straw but clamp the straw **a)** so no air can be exchanged between the two balloons. Then remove the peg (clamp) and what occurs is shown in **b)** with the smaller balloon collapsing completely into the larger balloon. Most people are very surprised by what actually occurs because they expect the air to equilibrate and become evenly distributed in both balloons. However, what is occurring is that the pressure of the air is equilibrating, not the volume, as air moves down in pressure gradient, as it always wants to do.

Newborn Respiratory Distress Syndrome (**NRDS**) typically occurs in premature babies, whose alveolar type II cells are not fully developed. Thus, they do not make adequate surfactant that is needed to prevent alveoli from collapsing, giving them low-compliance lungs and collapsing alveoli. This applies to all sizes of alveoli, recall that none of them should become too small, as the effort to re-inflate them becomes too high. Coupled with under developed respiratory muscles, the newborn babies have a very difficult time breathing normally and must expend a great deal of energy to re-inflate the collapsed alveoli every breath.

The condition known as **adult respiratory distress syndrome** (**ARDS**) is not related to surfactant production. In general, ARDS is caused by **pulmonary edema** that occurs when pulmonary capillaries become leaky to plasma proteins as a result of infection or autoimmune disease. The most common specific cause of ARDS is **sepsis**, which is an extreme and widespread infection of the bloodstream. It may be triggered by the inhalation of harmful substances. For examples, breathing in high levels of chemical fumes or any kind of smoke can result in ARDS. Getting anything into the lung tissue that does not belong there can make the pulmonary vasculature leaky which can lead to edema.

Pulmonary Function Tests Measure Lung Volumes during Ventilation

Physiologists and pulmonary specialists have developed some simple tests for determining proper lung function. Having a person breathe in and out under different circumstances is the basis of most of these tests. Here the focus is on the **spirometer**, other methods and equipment used to measure lung functions will also be discussed.

The spirometer is a piece of equipment that can measure lung volumes and capacities. From the results of these tests, certain pulmonary disorders can be detected.

Below in **Figure 18.21** is an illustration of a spirometer used very commonly in the past comprised of a 'floating drum' setup for testing a subject, and shows the trace (calibrated recording) from getting the subject to do simple breathing patterns. A spirometer is a diagnostic tool that measures the amount of air a person can breathe into and out of their lungs via a tube connected to this device. It can also measure the time it takes to exhale completely after taking a deep breath.

- The **upward** movement of the recording pen occurs during any **inspiration**.
- The **downward** movement of the pen occurs during any **expiration**.

Spirometers are used in physiology labs to measure the volume of moving air with each breath. Obstructive lung diseases involve diminished air flow during expiration due to narrowing of bronchioles.

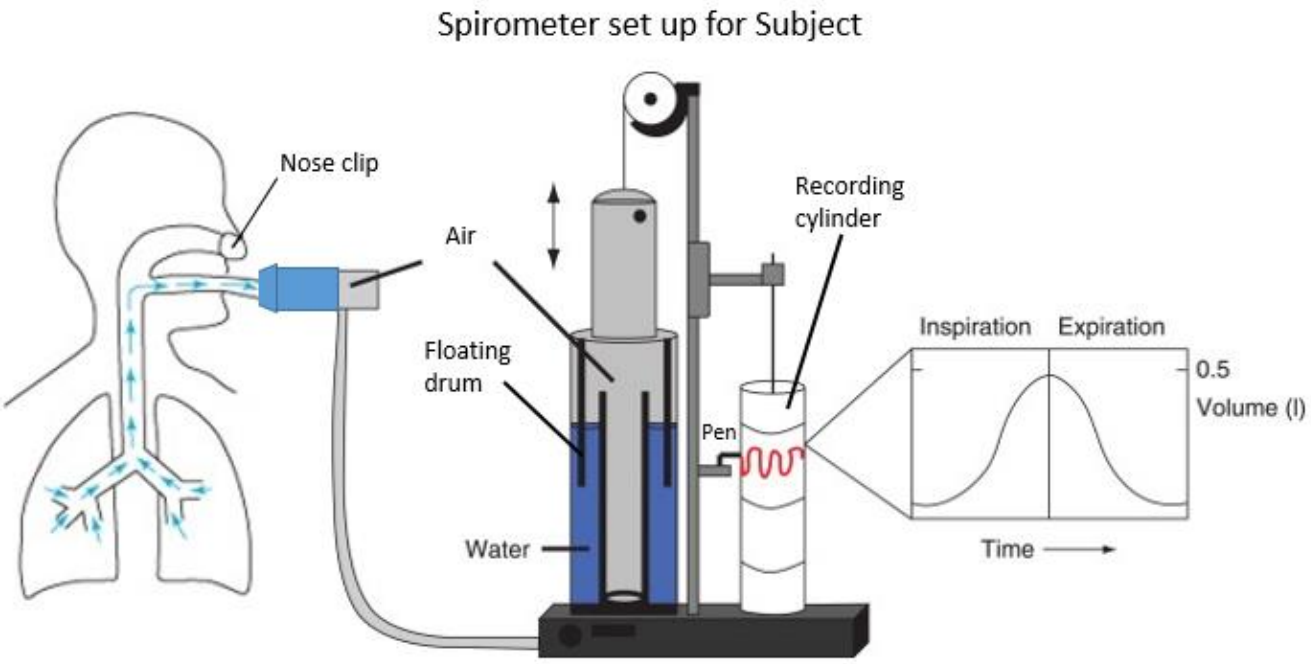


Figure 18.21 This illustrates the original set up of what was called a Bell Water Spirometer. The subject breaths only through their mouth into a tube connected to a floating drum creating a cylinder in water. The air breathed in makes the floating drum go down which is connected to a pen that gets deflected upward for inspiration which is connected to and recorded on the calibrated paper wrapped around a spinning cylinder. When the subject breaths out, it is a downward deflection for expiration d on the calibrated paper.

Spirometer Trace

The apparatus used, whether an 'old school' spirometer or a computerized version of that technology, will yield a recording of the changing lung volumes that will look somewhat like the trace shown below in **Fig. 18.22**.

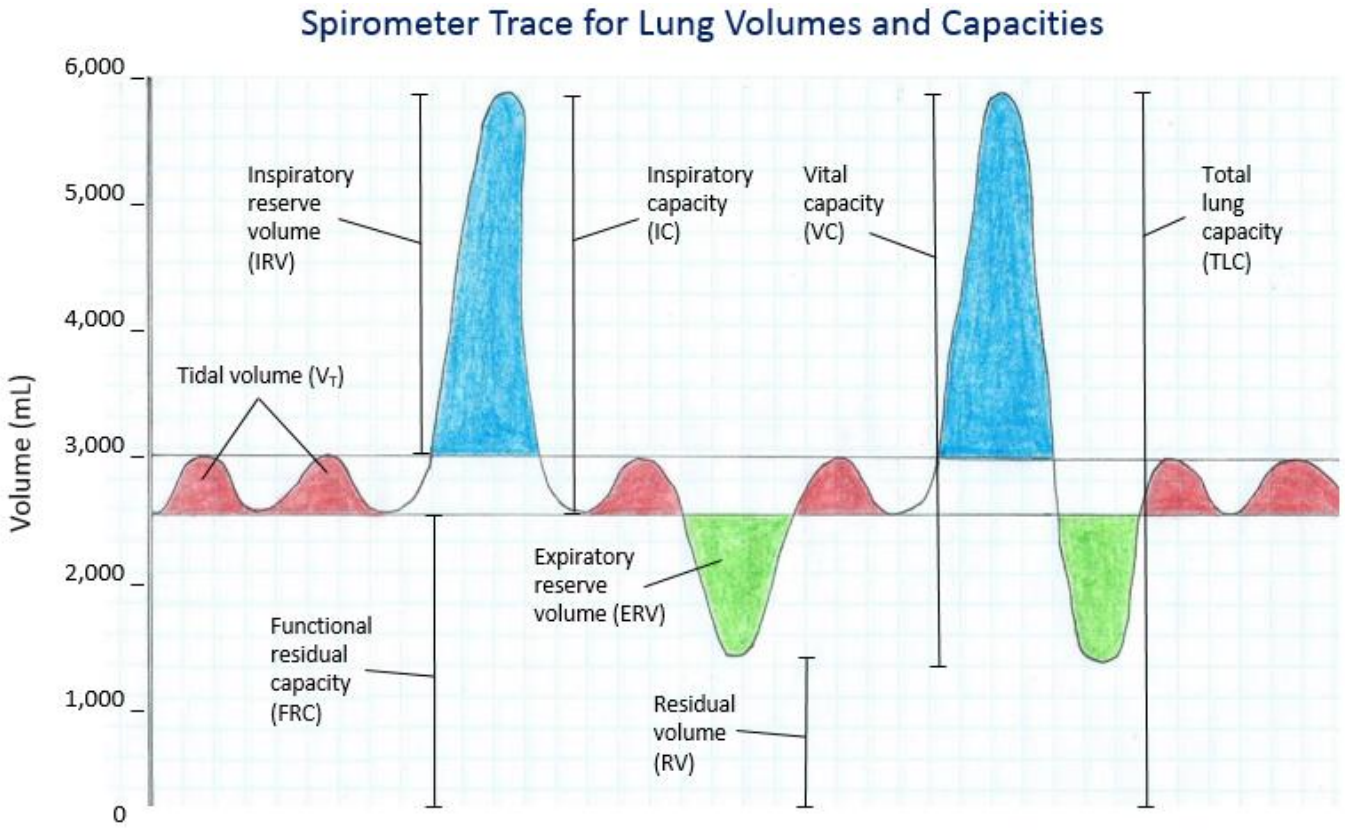


Figure 18.22 This is an example of a spirometer recording, showing the various lung volumes and lung capacities (ml) for a healthy 70Kg male subject. All breathing is occurring through the mouth only and the explanations for the various lung volumes and capacities seen in the spirometer trace above are described below.

Lung Volumes

A lung volume is something that can be directly measured on the spirometer. There are four lung volumes for air being moved during breathing:

1. Tidal volume (V_T): Air volume moving in a single normal inspiration or expiration.

2. Inspiratory reserve volume (IRV): Additional volume inspired above tidal volume.

3. Expiratory reserve volume (ERV): Air exhaled beyond the end of normal expiration.

4. Residual volume (RV): Air in respiratory system after maximal exhalation (not measured directly). It represents the air 'trapped' in the lungs, as the alveoli always retain air and never completely collapse. Residual volume can be measured by having the subject breathe helium, then calculating the dilution of the helium upon re-breathing room air.

Lung Capacities

Lung capacities are the sums (addition) of 2 or more lung volumes, and are therefore calculated volumes.

1. Total lung capacity (TLC) is the sum of all four volumes. Maximum volume of air voluntarily moved through respiratory system. VC + RV = Total lung capacity (TLC).

2. Vital capacity (VC) is the sum of IRV, TV, and ERV. In other words, VC is the maximal achievable TV and depends on the same factors discussed above for IRV and ERV. In patients with pulmonary disease, the physician may periodically monitor VC to follow the progress of the disease.
IRV + ERV + V_T = Vital capacity (VC).

3. Inspiratory capacity (IC) is the sum of IRV and TV. After a quiet expiration, the IC is the maximal amount of air that one could still inspire. V_T + IRV = Inspiratory capacity

4. Functional residual capacity (FRC) is the sum of ERV and RV and is the amount of air remaining inside the respiratory system after a quiet expiration. Because FRC includes RV, we cannot measure it using only a spirometer. ERV + RV = Functional residual capacity

Definitions of Pulmonary Volume Tests

It is useful to become familiar with the lung volumes and capacities shown in Fig. 1 above and how they might change in various lung disorders. For example, patients with restrictive lung disease such as **fibrosis** have a decreased inspiratory capacity. This is because of the reduced compliance of the lungs. Whereas patients with **emphysema**, who have lost elastic recoil cannot expel as much air during passive expiration, have an increased functional residual capacity as more air is trapped in the alveoli during expiration. Force expiratory volume (FEV_1) is the volume of air exhaled in the first second of forceful expiration and this can be measure with a peak flow meter. Those with **asthma** will have lower than normal FEV_1 values due to narrowed airways.

Auscultation of Breath Sounds

Breath sounds have a wide range of normal variation and are important to use as diagnostic tools, like heart sound auscultation. For example, air whistling through constricted airways produces the characteristic *wheezing* that accompanies an asthmatic attack.

Other Diagnostic Tests for Lung Function

- **Pulse Oximetry**
  Pulse oximetry measures O_2 levels in blood with a soft finger pad. The results are in percentage and this test can be done at rest, during exertion or sleep.

- **Arterial Blood Gases**
  A sample of blood is taken from the **radial artery** in wrist (sometimes femoral artery) to measure the O_2 and CO_2 levels in blood using a syringe with a thin needle.

- **Sleep Study (Polysomnography)**
  A sleep study is used to assess breathing throughout the night. Sensors attached to body monitor heart, lungs and brain, as well as the movement of some muscles. Test performed in a Sleep Lab overnight.

- **Body Plethysmography (Body Box)**
  Measures the volume of air in lungs that can be held, as well as how much air remains in lungs after breathing out. Can indicate if lungs are large or small, stiff or full of trapped air.

- **Diffusing Capacity**
  Test measuring the thickness of the membrane between the alveoli and blood vessels in your lungs. If alveolar membrane is too thick, the O_2 cannot pass as easily into blood.

- **Peak Flow Meter Spirometry**
  Measures the flow of air through lungs. If the airways are narrow, the air flows more slowly, making it harder to breathe. Take a deep breath in and blow out as hard and fast as possible.

- **Maximal Inspiratory/ Expiratory Pressure (MIPs and MEPs)**
  This test measures the strength of your breathing muscles, both inspiratory and expiratory. Taking a deep breath in against some resistance, then forcefully exhale against resistance.

- **Chest X-rays and CT scans**
  These can help visualize a detailed picture of lungs to rule out or confirm other problems such as pneumonia, tuberculosis or lung cancer. For example, emphysema shows large lungs with a low, flat diaphragm.

Rate and Depth of Breathing Determine the Efficiency of Breathing

Total pulmonary ventilation = the volume of air moved into/out of the lungs each minute. As examined in the lab, there is a formula to calculate total pulmonary ventilation, it is **Respiratory Rate** (breaths/min) times **Tidal Volume** (V_T), which has the units ml/breath. This gives a measure of effectiveness of ventilation. Typically the resting adult Respiratory Rate is from 12-20 breaths/min

Total Pulmonary Ventilation = RR x V_T

If RR =12 breaths/min and V_T = 500 ml/breath, then …
= 12 breaths/min x 500 ml/breath
= 6,000ml/min, or **6.0 L/min**

Total Alveolar Ventilation is a more accurate indicator of ventilation efficiency because it is a calculation of the air that gets to the alveoli, which is the site of gas exchange. In order to calculate values for this, the **anatomic dead space** must be accounted for and factored into the equation. The anatomic dead space is air that is trapped in the conducting airways and never makes it to the exchange region. It is estimated to be about **150 ml** of air, and that value is subtracted form tidal volume. Alveolar ventilation = Respiration Rate x (Tidal Volume - dead space volume).

Total Alveolar Ventilation= RR x (V_T -150)

Again, if RR =12 breaths/min and V_T = 500 ml/breath, then …
= 12 breaths/min x (500 -150) ml/breath
= 12 breaths/min x 35 ml/breath
= 4,200 ml/min or 4.2 L/min (vs. **6.0 L/min** for total pulmonary ventilation).

What we notice right away after testing both of the formulae is that total Alveolar Ventilation is always **less** than total Pulmonary Ventilation!

In some pathologies, there may also be **alveolar dead space**, that is, regions of alveoli that are being ventilated but not being perfused with blood. This might occur with low blood pressure, when the capillaries in the apex (top) of the lung are collapsed. The combination of *alveolar dead space* and *anatomic dead space* is called ***physiologic dead space***.

The Bicarbonate Buffer System

A buffer is typically a weak acid is solution that resists changes in pH, and thus acts to stabilize the pH even when acids or bases are added to solution. The **bicarbonate buffer system** is found in many region of the body, but is directly linked to the respiratory system in order regulate the pH of body fluids.

The reversible equation for this buffer is shown below and obeys the **Law of Mass Action** (or Le Châtelier's principle) in that the direction of this reversible equation is dictated by whatever is in excess (or deficiency) and it will drive the equation in the direction to make less (or more) of it, i.e. the equation strives to maintain equilibrium.

Figure 18.25 The bicarbonate buffer system is used in the respiratory system to control plasma pH by adjusting the [CO_2]. The equilibrium between dissolved CO_2 and H_2CO_3 is accelerated by the enzyme carbonic anhydrase, which catalyzes both the forward and reverse reaction (*). This reversible equation follows the Law of Mass Action to maintain equilibrium.

Respiratory Alkalosis and Acidosis

The condition of **respiratory alkalosis** is marked by a low level of carbon dioxide (CO_2) in the blood due to breathing excessively which removes the baseline CO_2 that triggers rhythmic breathing. This can result from hyperventilation (over-breathing beyond metabolic need), which can be brought on by anxiety or panic. Acutely it can cause light-headedness, confusion, paresthesias (nerve tingling), cramps, and syncope (fainting). Signs include hyperpnea (abnormally rapid or deep breathing) or tachypnea (involuntary rapid breathing) and carpopedal (wrist and feet, or fingers and toes) spasms.

The condition of **respiratory acidosis** occurs when the lungs cannot remove enough CO_2 from the body. This then causes the condition of **hypercapnia** (abnormally high CO_2 levels in body). Knowing the formula above in **Figure 18.25**, this excess CO_2 shifts the bicarbonate buffer to make more H^+ and causes the body fluids, like plasma, to become too acidic, which easily causes **metabolic acidosis**. This state of being too acidic happens to be the gateway to most disease states. Respiratory acidosis is caused by wearing a mask even for a short period of time as it restricts normal breathing. This condition can become a very serious condition, as the blood becomes more acidified, it may lead to increasingly serious symptoms, from mild feelings of **fatigue**, muscle twitches and headache, to loss of **consciousness** and **coma**. When experienced for short periods of time, it can clear up quickly on its own, but with severe hypercapnia, the body cannot restore normal CO_2 balance and the symptoms become more serious.

Gas Exchange in the Alveoli

Blood arriving at the lungs from the body tissues goes to the **alveolar capillaries** to drop off **CO_2** and pick up **O_2** before returning to the heart in the pulmonary veins. Once back in the heart, the newly oxygenated blood is subsequently pumped by the left ventricle into the systemic circuit to be perfused around the body again.

As blood courses through the lungs in the pulmonary capillaries, it weaves around the alveoli and is separated from the air in the alveoli by a very thin barrier, usually only 2 µm thick. The barrier is created by the thickness of the walls of the alveoli (type I alveolar cells) and the thickness of the walls of the capillary (endothelial cells). The way that the gases O_2 and CO_2 are exchanged between the pulmonary capillaries and the alveoli are down their partial pressure gradients.

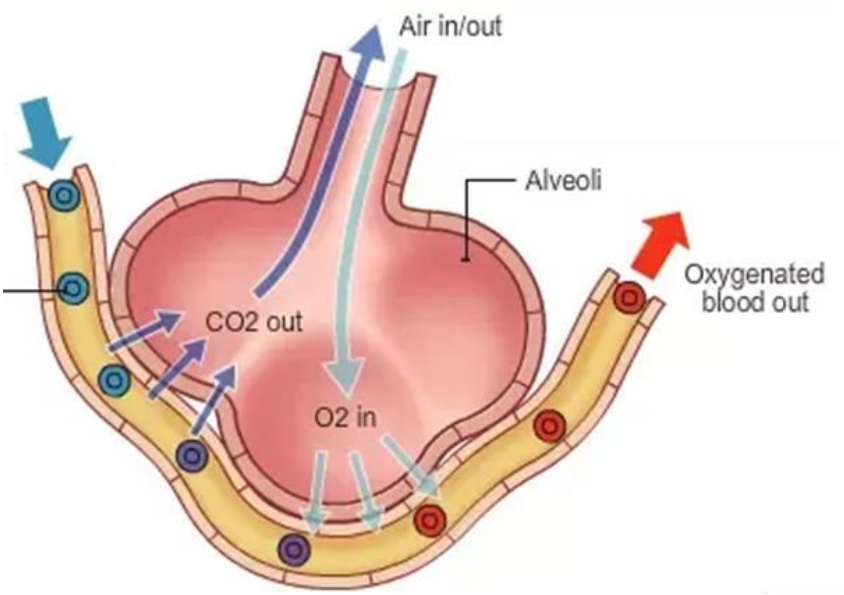


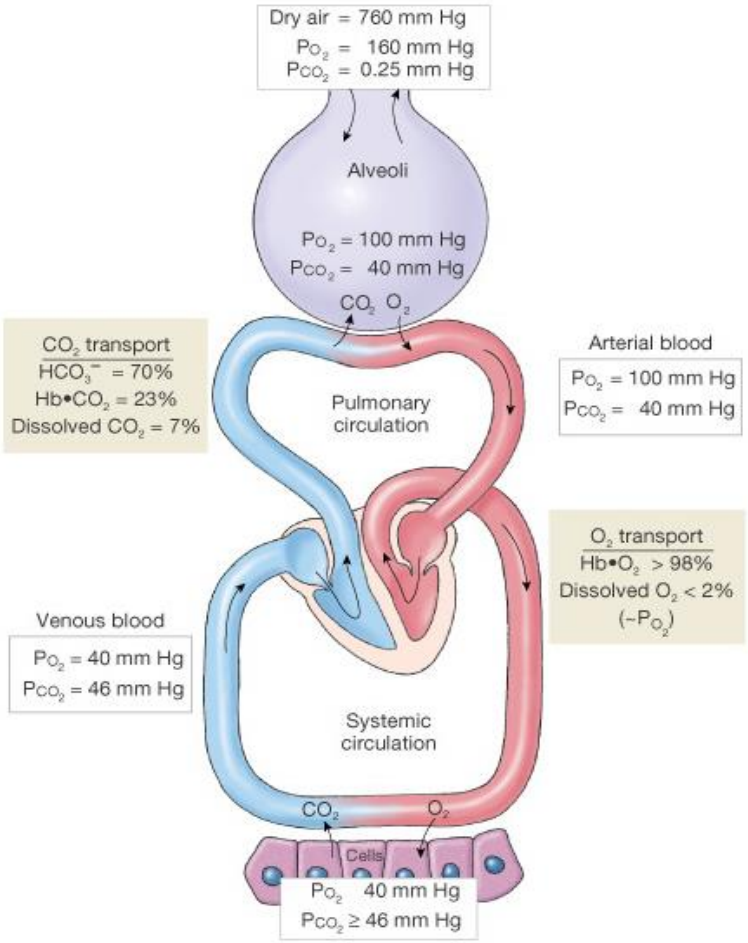
Figure 18.23 Shows the very close arrangement between the alveoli of the lung and the pulmonary capillaries that accomplished gas exchange. The incoming CO_2 rich and O_2 depleted blood entering equilibrate with the air in the alveoli with relative low CO_2 and high O_2 so the outgoing blood leaves it is CO_2 depleted and O_2 rich.

There are four basic values we need to know; O_2 and CO_2 levels in the capillary and the O_2 and CO_2 levels in the alveoli.

- The PO_2 levels as blood enters the pulmonary capillaries = **40 mmHg**
- The PCO_2 levels as blood enters the pulmonary capillaries = **46 mmHg**
- The PO_2 levels as blood leaves the pulmonary capillaries = **100mmHg**
- The PCO_2 levels as blood leaves the pulmonary capillaries = **40 mmHg**

Since the blood arriving in the alveolar capillaries has a P_{O2} **40 mmHg** while the P_{O2} of the air in the alveolar **100 mmHg**, there will be a net diffusion of O_2 from the alveoli into the capillary blood. In addition, in terms of the partial pressure of CO_2, the blood arriving to the pulmonary capillaries has a P_{CO2} of **46 mmHg** and the air in the alveoli is **40 mmHg**, thus there is a net movement of CO_2 out of the blood in the capillaries into the alveoli.

In the pulmonary capillaries, the partial pressures rapidly equilibrate with the gas pressures in the alveoli, this ensures that the arterial blood that circulates to all the tissues throughout the body has a partial pressure of O_2 (P_{O2}) is <u>100 mmHg</u> and the partial pressure of CO_2 (P_{CO2}) is <u>40 mmHg</u>.



These arterial partial pressures of O_2 and CO_2 are homeostatically controlled. A rise in the arterial P_{CO2} (and to a lesser extent a fall in the arterial P_{O2}) will cause deeper and faster breathing by reflex until the blood gases return to normal. The converse happens when the CO_2 tension falls (or, again to a lesser extent, the O_2 tension rises), the rate and depth of breathing are reduced till blood gas levels are restored.

Since the blood arriving in the alveolar capillaries has a P_{CO2} 46 mmHg while the pressure in the alveolar air is 100 mmHg, there will be <u>a net diffusion of O_2 into the capillary blood</u>. Similarly, since the blood arriving in the alveolar capillaries has a P_{CO2} of 46 mmHg and the alveolar air has a value of 40 mmHg, there is <u>a net movement of CO_2 out of the capillaries into the alveoli</u>.

Figure 18.24 The partial pressures of O_2 and CO_2 for the alveoli to pulmonary capillary (top), and the systemic capillary to the tissues (bottom) is shown. Both gases are always going down their partial pressure gradients, O_2 moving from the atmosphere to the alveoli, to the blood, and to the tissues, while CO_2. Moves form the tissues, to the blood, to the alveoli, and to the atmosphere.

<u>Note</u>: It is the CO_2 levels in the body that are the primary regulator of ventilation, and not O_2 levels. As we will see in the section regarding control of ventilation, the sensors in the body that detect dissolved gases in body fluid are the most sensitive to changes in CO_2, and the body never wants to eliminate all of the CO_2, that is dangerous. Here is an example: <u>Hyperventilation</u> (excessive ventilation beyond metabolic need) causes more CO_2 than usual to be blown out of the body and this signals respiration to slow down or even stop until the alveolar P_{CO2} has returned to 40 mmHg. Therefore, the primary function of the respiratory system is <u>not</u> to eliminate CO_2 from the body, but to keep stable levels of CO_2. Interestingly, there is far more CO_2 in the body than O_2, with about **26** mM total CO_2 in arterial blood compared to about **9** mM total of O_2. This demonstrates that CO_2 plays a critical role in the maintenance of pH of body fluids and that CO_2 is far more soluble than O_2 in body fluids.

Since O_2 has a very low solubility in water, it binds to the iron (Fe) containing heme groups within each globin subunit of the hemoglobin (Hb) molecule. When all the heme groups are bound with an O_2, it is said to be "saturated" with O_2. Most of the CO_2 in the blood is carried as HCO_3^- ions in the plasma. However, the conversion of dissolved CO_2 into HCO_3^- (through the addition of water) is fairly slow.

Therefore, this reaction is catalyzed by **carbonic anhydrase**, an enzyme inside the red blood cells. The reaction can go in either direction, depending on the prevailing partial pressure of CO_2. Some of the CO_2 (about 30%) is transported by the globin portion of Hb ($HbCO_2$), and called carbaminohemoglobin when it is in this state.

Optimal Conditions in the Normal Lung

Gas Composition in the Alveoli Varies Little during Normal Breathing

The values for P_{O2} and P_{CO2} can vary during hypoventilation and hyperventilation. The action of hyperventilation causes the P_{O2} to increase and the P_{CO2} to decrease. For hypoventilation, the P_{O2} decreases and the P_{CO2} increases. During normal breathing (eupnea), **the partial pressures of all gases remains fairly constant**. That is, P_{O2} = 100 mm Hg and P_{CO2} = 40 mm Hg. Why is this?

- One reason is that the fresh air entering the lungs is only about 10 to 20% of the total lung volume. It is estimated that per breath (in eupnea) only about 1/5 (20%) of the air in the alveoli is exchanged. Contrary to what you might initially believe, all the air in the alveoli is not completely 'changed out' each breath, but most of it is conserved. This helps to make the conditions inside the alveoli ***very stable***.

- In addition, the O_2 entering the alveoli is approximately equal to the O_2 entering blood. In this way, ventilation and perfusion are matched to ensure efficient exchange and delivery of gases. Oxygen transport in the blood is largely due to hemoglobin (Hb). The binding affinity of O_2 for Hb is affected by: pH, CO_2, temperature, and 2,3-DPG. These changes are reflected in the O_2-Hb dissociation curve discussed below.

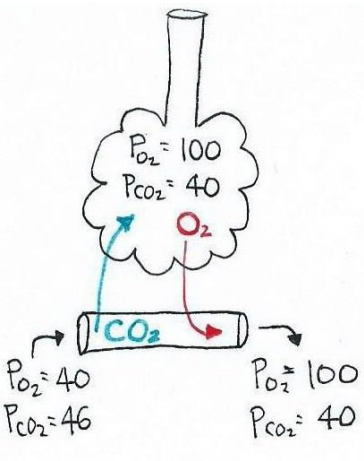


Figure 18.25 The sketch to the right shows that the blood entering the lungs has low P_{O2} and high P_{CO2} and theses levels become equilibrated with the alveolar values and the blood exiting the lungs now has high P_{O2} and low P_{CO2}.

Most of the CO_2 in the blood (about **60%**) is converted into $\mathbf{H^+}$ and $\mathbf{HCO_3^-}$ by the enzyme **carbonic anhydrase** inside RBCs. The reaction is: $\mathbf{CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-}$ (with $\leftrightarrow$ representing a reversible reaction arrow).

Therefore, body pH is related to P_{CO2} and ventilation. Respiration is under the control of a central pattern generator in the medulla oblongata and the pons. Chemical factors such as P_{O2}, P_{CO2}, and H^+ of body fluids will affect ventilation via the central and peripheral chemoreceptors. We can also exert conscious control over breathing, but not past the point of the chemoreceptor response. We will examine the regulatory control of respiration in the last section of these notes that focus on the factors that control ventilation.

Note: Lung **ventilation** is regulated by airway diameter, and **perfusion** is regulated by blood vessels. The bronchiole diameter is sensitive to changes in the partial pressure of CO_2 in the alveoli. If the partial pressure of CO_2 in the alveoli goes up, this causes bronchioles to dilate (increase diameter). In addition, a decrease in the partial pressure of O_2 in the blood will also causes bronchioles to dilate. This cumulatively augments exhaled CO_2 levels, as there is a need to get rid of more CO_2. If your body is producing more CO_2.

How Breathing can Change Body pH

If these mechanisms are compromised due to changes in breathing, then a **respiratory acidosis** (low pH, and high in CO_2 levels in the blood due to inadequate breathing), or a **respiratory alkalosis** (high pH, and low in CO_2 levels in the blood due to breathing excessively) can occur.

In the long run these can be compensated by renal adjustments to the H^+ and HCO_3^- concentrations in the plasma; but since this takes time, the hyperventilation syndrome can occur when agitation or anxiety cause a person to breathe fast and deeply. The effect of this is that there is too much CO_2 blown off from the blood into the outside air, and this precipitates a set of distressing symptoms (dizziness, confusion, numbness) which result from an excessively high pH of the extracellular fluids.

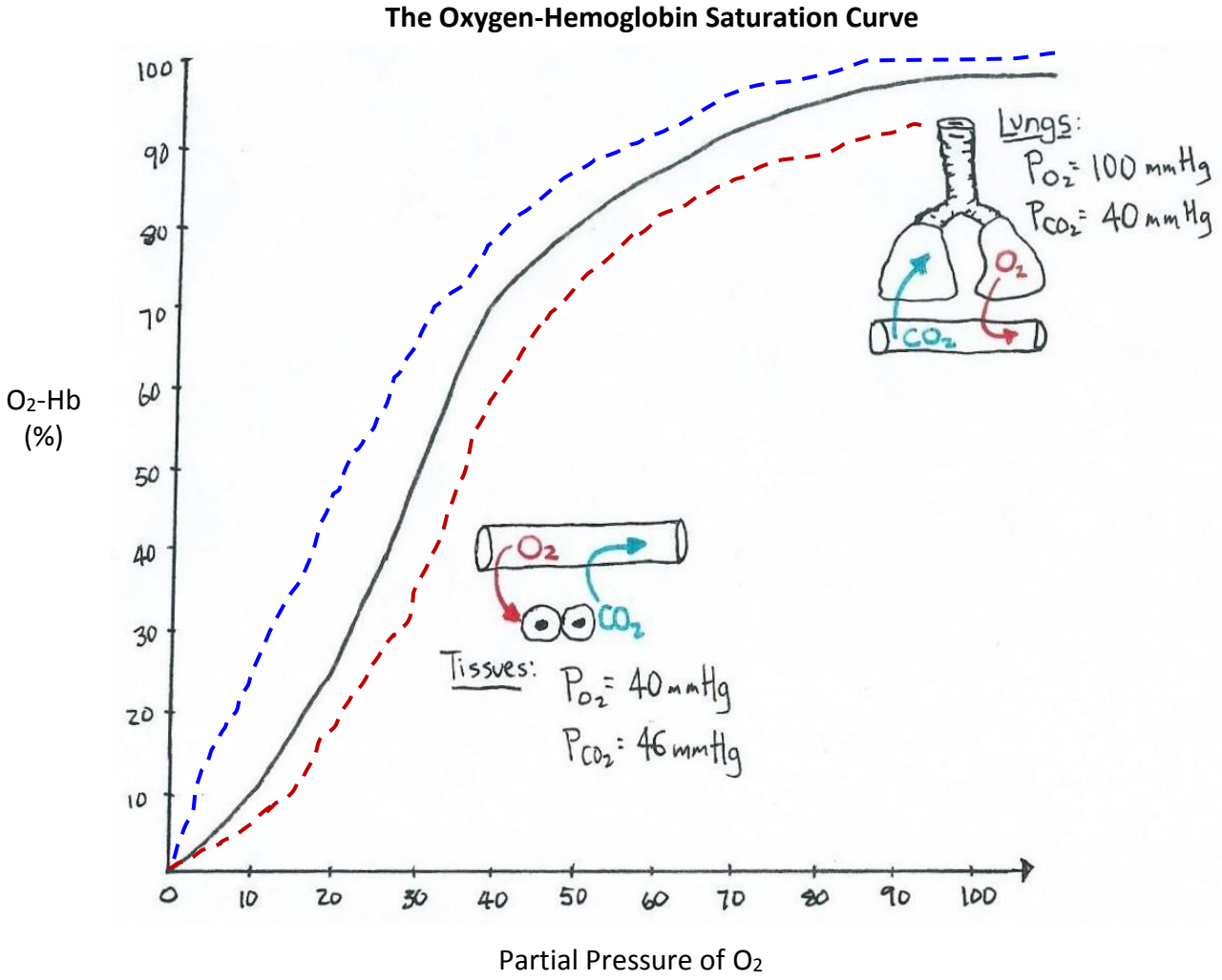


Figure 18.26 This is a graph of the Oxygen-Hemoglobin (O_2-Hb) saturation curve. It can also be described as the Oxygen-Hemoglobin dissociation curve. It shows the relationship between the Partial Pressure of O_2 (mmHg) and the percentage (%) of hemoglobin (Hb) that has O_2 bound to it. The central solid line is the normal curve. The blue dashed line is a left shift, and the red dashed line is a right shift.

Factors influencing the Affinity of Hb for O_2

The following physiological factors influence the affinity of hemoglobin (Hb) for oxygen (O_2) and therefore can cause O_2-Hb curve to "Shift":

- The pH of surroundings
- Body Temperature (T_b)
- The Partial Pressure of CO_2 (P_{co2})
- The amount of 2,3-DPG in erythrocytes

The four factors that shift the O_2-Hb curve (listed above) are very important and we will summarize them here. The basic premise is that any shift in this curve is in response to tissue needs throughout the body. First, there are basically two ways to shift this cure, to the **Left** and to the **Right**.

The best way to think of a Left Shift is when the body is less active metabolically and does not need as much O_2. Conversely, a Right Shift of the O_2-Hb curve occurs when the body is very active metabolically and has a much greater need for O_2. Examine both left and right shifts for the curve show in **Figure 18.26**.

We can use the example of when you are **sleeping** to discuss the **Left Shift** of the O_2-Hb curve in terms of the four factors.

As we Sleep:

- We have a decreased muscle activity (thus pH is higher or more alkaline).
- We are in a mini hibernation phase, thus are body temperature (T_b) decreases.
- Our entire body is resting, therefore much less active, thus the Partial Pressure of CO_2 is very low.
- There are no signals from the body to the RBC to make more DPG.

A more basic, or higher pH inhibits O_2 dissociation from Hb. As there is less O_2 is used by the body's cells in this state, the partial pressure of O_2 (P_{o2}) within most tissues remains relatively high, resulting in fewer O_2 molecules dissociating from Hb and entering the tissue interstitial fluid. Venous blood is said to be deoxygenated, but there is always some O_2 still bound to Hb in red blood cells, which can act as an O_2 reserve that can be used to provide more O_2 if tissue demand should increase.

We can use the example of when you are **exercising** to discuss the **Right Shift** of the O_2-Hb curve in terms of the four factors.

As we Exercise:

- We have a much greater muscle activity (thus pH is lower, or more acidic).
- We are highly active and muscle contraction generates heat, thus body temperature (T_b) increases.
- Many systems in our body are highly active, with many cells generating CO_2, thus the Partial Pressure of CO_2 is very high.
- There are numerous signals from the body to the RBC to make more DPG.

The pH of blood and surroundings influences the O_2-Hb saturation/dissociation curve. A lower, more acidic pH promotes O_2 dissociation from Hb. The greater the amount of CO_2 in the blood, the more molecules that must be converted, which in turn generates hydrogen ions and thus lowers blood pH. Furthermore, blood pH may become more acidic when certain byproducts of cell metabolism, such as lactic acid,

carbonic acid, and carbon dioxide, are released into the bloodstream. All of this pushes pH down and increases the release of O_2 from Hb and not the tissue that need it. The **Bohr Effect** describes this relationship between the pH and affinity of Hb for O_2.

Higher body temperatures promotes Hb and O_2 to dissociate faster. Highly active tissues use and release a larger amount of energy, some in the form of heat (2^{nd} law of thermodynamics). As a result, O_2 readily dissociates from Hb, which is a mechanism that helps to provide active tissues with more O_2.

As you can imagine, the more active your cells are the more CO_2 they make and the more O_2 they need. The active tissues (especially muscle) rapidly use O_2 to make ATP. This quickly lowers the partial pressure of O_2 (P_{O2}) to about 20 mmHg in the tissues. If the P_{O2} inside capillaries is about 100 mmHg, then the difference between the two regions (~80 mmHg) causes more O_2 molecules to dissociate from Hb so they can go to where they are less, into the tissues. Keep in mind that some tissues have a higher metabolic rate than others. In terms of laws or effects that are named after people, the **Haldane Effect** describes the relationship between the P_{O2} and the affinity of Hb for CO_2.

Certain hormones, such as testosterone, epinephrine, thyroid hormones, and growth hormone, can affect the O_2-Hb saturation/disassociation curve by stimulating the production of a compound called **2,3-diphosphoglycerate** (**DPG**) by erythrocytes (RBCs). As RBCs do not have any mitochondria, glycolysis is their only method to make ATP. DPG is a byproduct of glycolysis, and it promotes the decrease in the affinity that Hb has for O_2, or increases the rate of O_2-Hb dissociation. Therefore, the greater the concentration of DPG, the more readily O_2 dissociates from Hb.

In Summary, Hb has a higher affinity for O_2 when there is a Left Shift of the curve, and Hb has a lower affinity for O_2 when there is a Right Shift of the curve.

The Chloride Shift in the RBC

The chloride shift is an exchange process which occurs across the membrane of red blood cells (RBCs) as a way to assist in the transport of CO_2 in the cardiovascular system.

In the Tissues (peripheral capillaries)

In the body tissues, the Chloride Shift refers to chloride (Cl^-) ions entering the cell and bicarbonate (HCO_3^-) ions leaving the cell in order to pull in and transport CO_2 that normally builds up in tissues.

In the Lungs (pulmonary capillaries)

The opposite of this is the **reverse chloride shift**. This is what happens in the pulmonary capillaries as the (Cl^-) ions are now expelled from the RBC's and the HCO_3^- ions and brought into the RBC. This causes a shift in the bicarbonate buffer system which pushes out more CO_2 from the RBC at the lungs, releasing it into the alveoli so it can be exhaled.

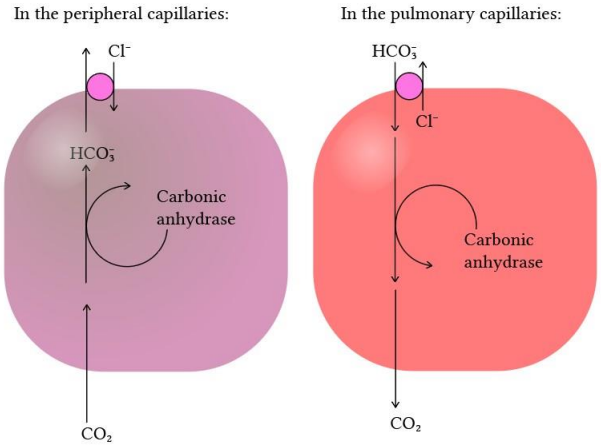


Figure 18.27 The actions of carbonic anhydrase seen in both peripheral (left) and pulmonary (right) capillaries.

How is Fetal Hemoglobin different form Adult Hemoglobin?

There is a difference between Adult Hb and **Fetal Hemoglobin** (**HbF**). Structurally, Hb-F is different from adult Hb and as a consequence it has a difference affinity for O_2.

The subunits for HbF are:

2 **α**-subunits and
2 **γ**-subunits (**γ** = gamma, not beta as it is in adult Hb!)

The effect of this structural difference is that functionally HbF binds to O_2 **with greater affinity** than adult Hb. In this way it advantages the capturing of O_2 by the developing fetus from the mother's bloodstream. Typically, by about 6 months old the newborn's HbF is virtually completely replaced by the adult form of Hb. The difference in O_2 affinity is due to the gamma subunits, which are different to beta by only a single amino acid (#143): HbF has serine instead of histidine, giving it a greater affinity for O2.

Effectively, the HbF does not interact with 2,3-DPG. As we already know, in adults 2,3-DPG is made by RBCs and decreases the affinity of Hb for O_2. In order for a mother to deliver more O_2 to her fetus, the HbF needs to extract more O_2 across the placenta. The technical reason for HbF more effectively grabbing the O_2 is because of the reduced positive charges of the γ subunit, which results in less electrostatic forces between the HbF and the 2,3-DPG, thus lowering the affinity for O_2. This lowered affinity allows for the adult (maternal) Hb to readily transfer its oxygen to the fetal bloodstream.

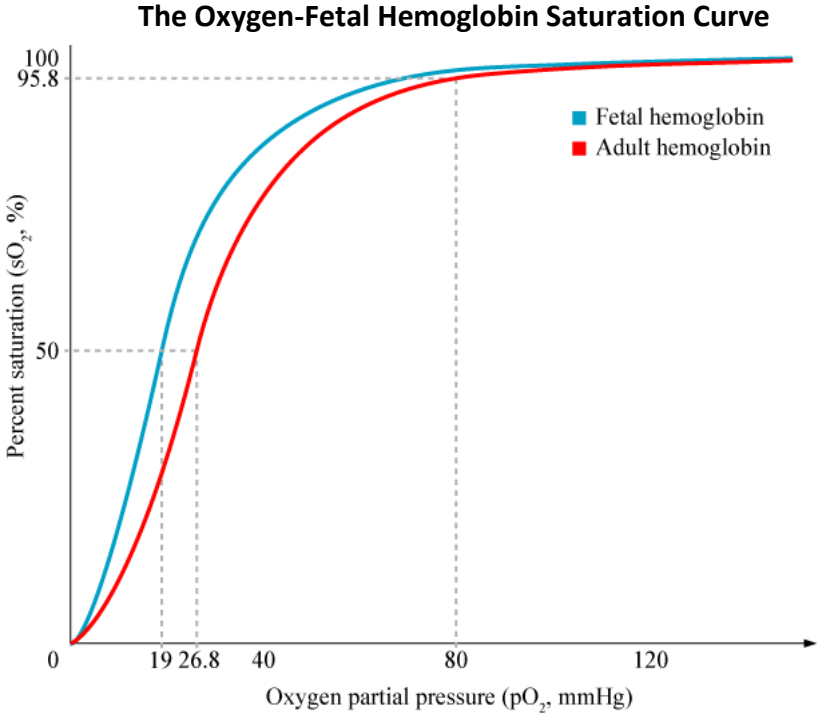


Figure 18.28 This graph compares of the Oxygen-Hemoglobin (O_2-Hb) saturation curve for fetal and adult Hb. The presence of fetal Hb effectively causes a left shift of the standard Oxygen-Hemoglobin (O2-Hb) saturation curve. Fetal Hb has a lower affinity of O2 and thus makes more O_2 available to tissue at lower P_{O2} values.

Many women experience anemia while pregnant. The 2,3 DPG levels begin to rise early in pregnancy and this results in a gradual shift to the right in the maternal O_2-Hb dissociation curve and therefore an increase in the amount of O_2 unloaded in the peripheral tissues, including the intervillous space of the placenta

(which is the area between the villi containing the vessels of the mother and the embryo). This facilitates O_2 transfer from mother to fetus. The pregnant mother has a **lower hematocrit** and produces **more 2,3 DPG** in order to off-load more O_2 into the placenta. The fetal hematocrit is also very high, at around 55% to 65%. *This allows fetal blood to pick up more O_2*. These factors facilitate a very efficient O_2 transfer at the placenta to the developing baby.

Table 18.1. Shows differences in hematocrit with gender and age.

Sex and Age Differences	Normal Hematocrit Range
Males	**42% to 52%**
Females	**36% to 45%***
Children	**36% to 40%**
Fetus/Newborn	**55% to 65%**

*lower during pregnancy

How 2,3-DPG works and the strategies of Fetal Hb

The 2,3-DPG molecule has its effects by siting in the middle of the Hb molecule where it preferentially binds to the beta subunits. This causes confirmation changes in the Hb molecule that prevent the 2.3-DPG from binding to it.

The levels of 2,3-DPG go up in situations where you need more O_2. What would some of those situations be? They could be: **a)** high altitudes; **b)** chronic lung diseases that decrease O_2 levels; and **c)** anemia. If for one of these reasons the tissues are lacking sufficient O_2, then the RBCs would make a more 2,3-DPG, since this would allow the Hb to release more of the O_2 it holds and deliver it to the tissues.

The Control of Respiratory Ventilation

This will be covered in the next chapter, but in general and for the most part, breathing occurs without conscious thought. There are many times that it will be under conscious control, for example, a loud sigh to indicate boredom, or holding your breath when submerging your head below water, or blowing out birthday candles. All occur due to deliberate thought and control of breathing. However, the vast majority of breathing patterns during rest and activity are highly automated.

The **respiratory rate** is the total number of breaths, or respiratory cycles, each minute. Respiratory rate can be an important indicator of health, as the rate may increase or decrease during an illness or in a disease condition. As will be discussed in detail in the next section, the rhythmic respiratory rate is controlled by the **respiratory control center** located the **medulla oblongata.** As we will see, it responds primarily to changes in CO_2, pH levels in the blood and cerebrospinal fluid (CSF) and O_2. The pons is the other region of the brain that contains respiratory centers, and is for fine tuning and protection of the lungs.

Common Lung Conditions, Disorders and Diseases

Listed and described below are some of the most common lung conditions, disorders and diseases that allied health professionals may come across in their field. In some instances, the pulmonary disorder may arise as a secondary consequence of another primary ailment.

Note on Etymology: It is very helpful to look up the **word origin** (etymology) for the terms (word or words) used in any of the ailments listed below, especially if you have never heard of them or do not know what they actually mean. For example, **empyema** and **emphysema** are very different conditions, though they look and sound similar. Understanding the origins of these words will highlight and help in understanding the important differences in the two disorders. The 'pye' in empyema comes from puon, which means pus. There is only pus in empyema, not in emphysema (which means to puff up).

Asthma - is an allergic inflammatory condition characterized by severe constriction of the bronchioles (which are the airways within the lungs), and this is called ***bronchoconstriction***. It is also often accompanied with inflammation of the airways and increased mucus. These conditions significantly restrict air flow due to the decrease in airway diameter. The subsequent increased resistance to the flow of air particularly inhibits passive expiration, as typically this does not required muscle contraction. Histamine release is a central trigger in the bronchoconstriction of asthma. Leukotrienes (lipid-like eicosanoid inflammatory mediators) are also secreted by mast cells, macrophages, and eosinophils during the inflammation and cause bronchoconstriction. An asthma attack can be triggered by allergic reactions, infections, irritant (pollution) cold air, and stress. This is a reversible condition and can be resolved (without medication).

In some instances, a massive bronchoconstriction of an asthma attack or allergic reaction can be fatal. The quick administration of an **epinephrine injection or a **beta-agonist** inhaler such as ephedrine or isoproterenol induces **bronchodilation** that relieves the problem.*

Emphysema - involves the **destruction of lung tissue**, which reduces both the surface area for gas exchange, and reduces the elasticity of the lung tissue, due to elastin fibers being destroyed. The vast majority of emphysema is from chronically inhaled irritants that over stimulate **alveolar macrophages** which then release **trypsin** (a digestive enzyme) and damage lung tissue. The macrophages are present to protect the alveoli but when they become overactive can cause damage. A small % of emphysema cases are caused by a genetic disorder in which type I alveolar cells (simple squamous epithelium) cannot make the substance **alpha-1 anti-trypsin**, this is a substance which covers alveolar cells (analogous to floor wax on the tiles of a floor) to protect them against the normal trypsin exposure. If cells are deficient or lack the anti-trypsin, they are much more vulnerable to degradation by trypsin.

**Emphysemic lungs have high compliance and low elastance. They exhibit poor recoil during expiration (exhaling). Lungs become even more compliant but less elastic, resulting in a hyper-inflated lung and the "barrel-chest" associated with chronic emphysema. The need to over-use expiratory muscles may also contribute to the barrel chest. Since in eupnea there is no muscle contraction required to exhale, normally only about 3% of the basal metabolic rate (BMR) is used to for ventilation/respiration. However, in those with emphysema, breathing requires about 30% of BMR.*

Chronic Bronchitis – this is **inflammation** of the **bronchioles** of the lung over a long period of time. It is accompanied with **excessive mucous production**. People can develop acute bronchitis from inhaled irritants or from a viral or bacterial infections. Often the overproduction of mucus is an attempt to protect the lung tissue, but can immobilize the cilia that line the respiratory tract to keep mucous moving. The lack of mucous movement due to inactive cilia can result in stagnant mucous; this creates a rich source energy for bacterial growth. This can make recurrent bronchitis a common cycle and become long term.

Both **emphysema and **chronic bronchitis** are considered COPD's.*

Pneumonia - this is an inflammation of the air sacs (alveoli) in the lungs. Thus it is deeper in the respiratory system than bronchitis. It can be caused by bacterial, viral, fungal, or parasitic infections, medications or autoimmune disorders. It is a type of **pneumonitis** (inflammation of the lungs) which hampers gas exchange. Rarely, it may result in an accumulation of fluid the space that surrounds the lung (the plural cavity).

Tuberculosis - caused by bacteria called **Mycobacterium *tuberculosis***. Alcohol abuse, diabetes mellitus, medications (corticosteroids, infliximab for Crohn's disease), poor nutrition and stress can vastly increase the likelihood of getting this (and any) disease. It involves inflammation of the **alveolar sacs** of the lungs.

Cystic Fibrosis - this is a genetic disorder affecting several organs. In the respiratory system, a defective gene changes chloride ion (Cl^-) channels and this results in **overly thick and sticky mucus** that obstructs bronchioles and airway passageways. This excess mucus causes recurrent lung infections. This disorder also involves the pancreas and creates obstructions there, preventing important chemical (enzymatic) digestion of nutrients in the gastrointestinal tract.

Bronchiectasis - this is a condition involving **abnormally dilated bronchial tubes**. Most commonly it enables mucus to pool, promoting respiratory tract infections, wheezing and shortness of breath. Often develops from cystic fibrosis, but can have other causes.

Pleural Effusion - is occurs when there is an **accumulation of fluid in the pleural cavity**. This restricts the expansion of the lungs, thus ventilation, and can lead to shortness of breath. It can be caused by pneumonia or congestive heart failure. Effusion means a 'pouring forth'. It is restrictive.

Empyema - this is an infection and **accumulation of pus of the pleural fluid in the plural cavity** that surrounds the lungs. The etymology of this word is from Greek, *em- or en* meaning entry, and *pyon* meaning pus. It is often associated with pleural effusion.

Pulmonary Fibrosis - occurs when lung tissue becomes damaged and **scarred**, resulting in a **thickening** of the tissue, especially the alveolar walls. This makes the lung stiff and more difficult to stretch and expand, leading to low compliance, as it will require more energy to stretch fibrotic lungs. For this reason, this is often referred to a '**stiff lungs**'. Transfer of gases across the alveolar wall are hampered by the increased thickness of the barrier. Inhaled irritants can cause fibrosis of the lungs.

**Pulmonary compliance is the ease with which the lungs can be stretched. It is related to the amount of work required to stretch the lung (inhale). The less work required the more compliant the lungs are. Lung compliance is inversely proportional to elastance. Both compliance and elastance are important properties of lung tissue and must be balanced for healthy functional lungs*

Pulmonary Edema - occurs when there is **excess fluid volume that accumulates in the interstitium** (tissue spaces) of lungs. This increase in tissue fluid volume increases the distance between the alveoli and the pulmonary capillaries in the lung. It is deleterious because gas exchange is impaired. This fluid collects in the numerous air sacs in the lungs, making it difficult to breathe. It is a characteristic of congestive heart failure and can lead to fatal respiratory distress or cardiac arrest due to hypoxia (low O_2). It also restricts the ability of the lung to expand and is considered a restrictive lung disease.

Pneumothorax - is a **collapsed lung**, due to a disruption in the sub-alveolar pressure in the plural cavity needed to keep the lungs stretched (even during exhaling) maintain the transmural pressure gradient. It can be the result of trauma to the lung (a puncture wound) known as a ***traumatic pneumothorax***; or it can be from internal changes, known as a ***spontaneous pneumothorax***.

Atelectasis - is when one or more lobes of the lung collapse due to a **blockage or pressure within or outside of the bronchial tubes in the lungs**. This type of blockage traps air in the lungs creating a sensation of shortness of breath. The blockages can be caused by a mucus plug, an inhaled object, or abnormal tissue growth (tumor). The etymology of this word is from Greek ateles = imperfect, incomplete; ektosis = extension (ek= out of, from); and teinein = to stretch. Altogether it means "incomplete expansion of the lungs".

Lung Cancer - this is **uncontrolled growth of abnormal, undifferentiated cells** in lung tissue, hampering function. It often develops near the air sacs.

Pulmonary Hypertension - refers to elevated lung and right ventricular blood pressure. This occurs when the pressure in the blood vessels leading from the heart to the lungs is too high. With pulmonary hypertension, the blood vessels to the lungs develop an increased amount of muscle in the wall of the blood vessels. It may also lead to pulmonary edema as more fluid than usual is filtrated out of the pulmonary blood vessels, which hampers oxygen (O_2) and carbon dioxide (CO_2) exchange in the lungs.

Sinusitis - this is inflammation of mucous membranes in the **para-nasal sinuses**. Recall the suffix (at the end of a word) –itis means inflammation of swelling. These sinuses are cavities in the bones of the skull that produce mucus, lighten the weight of the skull and provide sound resonance. The commonly inflamed sinuses are the maxillary sinuses that are on either side of the nose, but also involve the frontal, sphenoidal and ethmoidal sinuses. Nasal sinuses can experience increased pressure. Congestion and discomfort. It can also cause headaches and a reduction in olfaction (the sense of smell).

Having read the examples above, it may be seen that, in general, many common lung disorders can be in either one of two broad categories, they are **Chronic Obstructive Pulmonary Diseases**, often stated as COPD's, and **Restrictive Lung Disease**. These are important clinical distinctions in that one set of disorders involves 'obstruction' or 'blockage' of the airways in various capacities (and over extended periods of time), while the other involves a 'restriction' of lung tissue, in contrast to the normal natural healthy recoil and flexibility of the lung tissue. It is possible that both of these conditions can exist at the same time

Chronic Obstructive Pulmonary Disease (COPD)

Any designation of a chronic obstructive pulmonary disease (CPOD) is an umbrella term that encompasses several chronic inflammatory lung diseases that cause obstruct airflow within the lungs. These respiratory illnesses **increase airway resistance**, due to chronic inflammation and mucus production. Diseases that are considered COPD's include **emphysema** and **chronic bronchitis**. Often asthma is not considered a COPD, because unlike COPD's asthma, is reversible.

Restrictive Lung Disease

Conditions that involve restrictive lung disease result in an inability to fully expand (stretch) the lungs, thus they cannot fill with air. These disorders exhibit **reduced compliance**, in that more work than normal is required to stretch the lungs. It makes sense that any pulmonary restriction involving lungs that are stiff would require more work to inflate (stretch) them. This can result from inelastic scar tissue, insufficient pulmonary surfactant, weak respiratory muscles and damaged nerves. Other conditions that can cause restrictive lungs are **pulmonary edema**, **pulmonary fibrosis**, sarcoidosis (autoimmune disease) and obesity.

Review Questions for Chapter 18: The Respiratory System

1. When the diaphragm and the external intercostals contract
- **a)** the volume of the thoracic cavity increases
- **b)** the volume of the thoracic cavity decreases
- **c)** the volume of the lungs decreases
- **d)** the pressure of the thoracic cavity increases
- **e)** expiration occurs

2. Which of the following would cause more gas to dissolve in a liquid solution?
- **a)** a decrease in the partial pressure gradient
- **b)** an increase in temperature of the solution
- **c)** a decrease in temperature of the solution
- **d)** a decrease in pH of the solution

3. The values (mm Hg) for P_{CO2} and P_{O2} inside the alveoli are approximately:
- **a)** 60: 40
- **b)** 40: 100
- **c)** 46: 40
- **d)** 66: 46
- **e)** 46: 100

4. In the *respiratory system*, sympathetic stimulation of *bronchioles* results in
- **a)** asthma
- **b)** an increase in blood pressure
- **c)** bronchoconstriction
- **d)** bronchodilation
- **e)** vasoconstriction via α receptors

5. Which of the following reactions takes place in the **systemic capillaries**?

a) $HbO_2 \rightarrow Hb + O_2$
b) $HbCO_2 \rightarrow Hb + CO_2$
c) $Hb + O_2 \rightarrow HbO_2$
d) $CO_2 \rightarrow H_2O + H^+$

6. Water molecules on the surface of the alveoli generate surface tension: this force

a) assists pulmonary compliance
b) assists elastic recoil
c) resists elastic recoil
d) inhibits alveolar collapse
e) impairs gas exchange

7. Type I alveolar cells

a) make surfactant
b) stabilize the size of alveoli
c) create the walls of alveoli for gas exchange
d) release trypsin, a powerful chemical that degrades proteins
e) phagocytose cells

8 Fibrotic lung disease involves

a) a thickening of alveolar wall
b) increased alveolar pressure
c) a decrease in gas exchange
d) an increase in surface area available for gas exchange
e) both a and c

9. Apnea means:

a) holding ones breath instead of breathing
b) inflammation of the airways
c) an increase in breathing rate
d) a cessation (stopping) of breathing
e) starting up of breathing after holding one's breath

10. For alveolar macrophages, which are true? Select all that apply.

1. They release anti-trypsin
2. They phagocytose particles
3. Their actions oppose surfactant
4. They release trypsin
5. They release mucus

Answers in Appendix B