

The main functions of the respiratory system include:

1. Exchange of **O₂** and **CO₂**.
2. Voice production.
3. Regulation of **plasma pH**.
4. **Olfaction** (sensation of smell)
5. Infection (pathogen invasion) prevention.

Respiration is associated with 4 processes:

1. **Pulmonary ventilation** is the movement of air into/out of the **lungs**
2. **External respiration** is the movement of O₂ from the lungs to the **blood** and CO₂ from the blood to the lungs.
3. **Gas transport** refers to the mechanisms by which O₂ and CO₂ are moved thru the blood.
4. **Internal respiration** is the movement of O₂ from the blood to the **cell interior** and CO₂ from the cell interior to the blood.

Cellular respiration is the breakdown of **glucose, fatty acids** and **amino acids** that occurs in **mitochondria** and results in production of **ATP**. It requires O₂ and produces CO₂. (Note that this type of cellular respiration, which requires O₂, is known as “**aerobic metabolism**,” whereas breakdown of glucose that produces ATP but does not require O₂ is “**anaerobic metabolism**.”)

The structures of the respiratory system can be divided into the **upper respiratory tract** and the **lower respiratory tract**. The upper respiratory tract refers to the **nose, pharynx**, and their associated structures. The lower respiratory tract includes the **larynx, trachea, bronchi**, and **lungs**.

The respiratory system can also be separated into a **conducting zone** and a **respiratory zone**. The **conducting zone** refers to structures that transport air but play no role in gas exchange. It includes: **nasal cavity, nasopharynx, oropharynx, laryngopharynx, larynx, trachea, bronchi**, and all **bronchioles** except for **respiratory bronchioles**. These structures are involved in transporting, filtering, humidifying, and warming air.

The **respiratory zone** refers to structures where exchange of O₂ and CO₂ occurs. Sites of exchange are known as **alveoli** (sing. **alveolus**). All respiratory zone structures contain alveoli and include: **respiratory bronchioles, alveolar ducts**, and **alveolar sacs**.

The **nose** is divided into the **external nose** and the **internal nasal cavity**. Air enters the nasal cavity via the **nostrils** or **nares**. The initial space just beyond the open is the **nasal vestibule** and it contains **vibrissae** (hairs) which perform a filtration function. The nasal cavity is divided by the **nasal septum**. The nasal septum is formed anteriorly from **septal cartilage**, and posteriorly from the **perpendicular plate** of the **ethmoid bone**, and the **vomer**. The **sphenoid** and **ethmoid bones** form the roof of the nasal cavity. The **hard palate** forms the floor of the nasal cavity. It is composed of the **palatine processes** of the **maxillary bones** and the **horizontal plates** of the **palatine bones**. The lateral walls of the nasal cavity are composed of the maxillae as well as the 3 pairs of **nasal**

conchae. The **superior** and **middle nasal conchae** are projections of the **ethmoid bone**. The **inferior nasal conchae** are bones of their own. Nasal conchae increase the surface area of the nasal cavity and make airflow turbulent. The turbulence decreases the velocity of airflow. The resulting increased amount of time coupled with the large surface area allows the inspired air to be filtered, warmed, and humidified.

The majority of the nasal cavity is lined by **respiratory epithelium**. Respiratory epithelium is **pseudostratified columnar epithelium with goblet cells**. The **mucus** secreted by goblet cells, as well as by mucous glands, helps filter and trap inspired particulate matter. The moist mucus (as well as the watery solution secreted by **serous glands**) contributes to the humidification of inspired air. Cilia help sweep mucus to the pharynx where it is swallowed. Respiratory epithelium is underlain by a dense vasculature. The blood helps warm inspired air. Mucus also contains **lysozyme** as well as immunoglobulins, which help prevent infection. The **olfactory epithelium** is located in the most superior region of the nasal cavity and is involved in olfaction. The nasal cavity is continuous with the nasopharynx via the **posterior nasal apertures**.

The **paranasal sinuses** are cavities within the bones surrounding the nasal cavity. There are a total of 5 sinuses: **ethmoid sinus**, **sphenoid sinus**, **frontal sinus**, and the paired **maxillary sinuses**. Paranasal sinuses contribute to mucus production, lighten the skull, and provide resonance during speech. Openings from the paranasal sinuses empty into the nasal cavity. The 2 **nasolacrimal ducts** also empty (drain tears) into the nasal cavity.

The **pharynx** is the common portion of the respiratory and digestive tracts. It receives air from the nasal cavity and food, drink, and air from the oral cavity. It's continuous with the resp. tract at the larynx and with the digest. tract at the esophagus. The pharynx is divided into 3 sections: **nasopharynx**, **oropharynx**, & **laryngopharynx**. The nasopharynx extends from the posterior nasal apertures to the end of the **soft palate** and is lined by respiratory epithelium. The **soft palate** is the partition btwn the nasopharynx and the oral cavity. It's primarily composed of skeletal muscle. The posterior-most portion that hangs down is the **uvula**. The soft palate and uvula flip up during swallowing and help prevent food/drink from entering the nasopharynx. On the lateral walls of the nasopharynx are the openings to the **auditory tubes** (a.k.a. **Eustachian tubes**). Each auditory tube connects the pharynx to a **middle ear cavity**. They ensure that air pressure within the middle ear cavities is equal to atmospheric pressure. The nasopharynx also contains the **pharyngeal tonsil**.

The oropharynx is inferior to the uvula and superior to the **epiglottis**. It's posterior to the oral cavity and is continuous with it at an arched region known as the **isthmus of the fauces**. 2 sets of tonsils (**palatine** and **lingual**) are located right nearby. It's lined by nonkeratinized stratified squamous epithelium. This provides the necessary protection since this region is a common pathway for food and air.

The laryngopharynx is inferior to the epiglottis and superior to the split between the larynx and the esophagus. It's lined by nonkeratinized stratified squamous epithelium b/c it is also a common pathway for food and air. It's continuous with the larynx inferiorly.

The **larynx** routes food and air down their correct passages. It contains the **vocal cords**, which function in voice production. The larynx is a tube made up of 9 cartilages connected by membranes, ligaments, and muscles. The cartilages include **thyroid, cricoid, epiglottis** and 3 small, paired cartilages (**arytenoids, cuneiforms, and corniculates**). All the laryngeal cartilages are hyaline cartilage with the exception of the epiglottis, which is elastic cartilage. The thyroid cartilage is the largest and its midline **laryngeal prominence** is the “**Adam’s apple**.” The thyroid cartilage is just inferior to the **hyoid bone**. Inferior to the thyroid is the signet ring-shaped cricoid cartilage. It forms the base of the larynx. The epiglottis extends from the superior thyroid cartilage with its free flap abutting the tongue. During swallowing, the epiglottis tips and covers the entrance to the larynx and ensures that food enters the esophagus. Deep to the laryngeal mucosa in the lateral walls of the larynx are the **vocal ligaments**. They extend from the arytenoids cartilages to the posterior surface of the thyroid cartilage. These are the core of the **vocal folds** or **true vocal cords**. Vibration of the vocal ligaments creates sounds that are then modified by the tongue, lips, etc., to produce speech. Skeletal muscles move the arytenoids and other cartilages and change the position and tension of the vocal cords (this modifies the sounds produced). The tension of the vocal cords is directly related to the pitch of the voice. The amount of air rushing past the vocal cords is directly related to the loudness of the voice. Superior to the vocal folds are the **vestibular folds** or **false vocal cords**. These play no role in voice production. They help prevent food particles from passing thru the larynx as well as provide lubrication for the vocal folds. The space between the vocal folds on the left and those on the right is known as the **glottis**. Closure of the glottis during expiration (i.e., the **laryngeal sphincter action**) allows for a large increase in thoracic and abdominal pressure. The larynx is lined by respiratory epithelium below the vocal folds. The remainder is lined by stratified squamous epithelium.

Continuous with the larynx inferiorly is the **trachea**. It has a mucosa lined by respiratory epithelium, a submucosa of CT, and a smooth muscle layer all reinforced by 15-20 C-shaped rings of hyaline cartilage. It’s surrounded by a dense adventitia. It extends from the larynx to the mediastinum, where it splits into 2 **main bronchi**. The trachea is associated with copious mucus secretion – due to its abundant **seromucous glands**. Its rings prevent it from collapsing during inspiration. The open portion of the C is posterior and houses the **trachealis muscle**. Its contraction can alter the radius of the trachea and it plays a large role in coughing. The lack of posterior cartilage is important b/c it provides the esophagus with room to expand when a large bolus of food is swallowed. The last tracheal cartilage is expanded and contains a very sensitive posterior projection known as the **carina**.

The trachea divides into 2 **main bronchi**. The right main bronchus is wider, shorter, and more vertical than the left. It’s more likely to be obstructed by a foreign object. Air reaching the bronchi has been significantly filtered, warmed, and humidified. Within the lungs, each main bronchus divides into **lobar bronchi**. There are 3 lobar bronchi on the right (one for each of the 3 **lobes** of the right lung) and 2 lobar bronchi on the left (one for each of the 2 lobes of the left lung). Lobar bronchi divide to yield **segmental bronchi**

that divide to yield smaller and smaller bronchi until about 23 branchings have occurred. Once the passageways have a diameter <1mm they are known as **bronchioles**. The **terminal bronchioles** are the last bronchioles without **alveoli**. Bronchioles with alveoli are known as **respiratory bronchioles** and lead into **alveolar ducts**.

As the bronchial tree branches, its histology changes markedly:

1. Cartilage rings are replaced by cartilage plates, and within the bronchioles, cartilage is absent entirely.
2. Epithelium changes from pseudostratified columnar to simple columnar to simple cuboidal.
3. The number of cilia declines.
4. The number of goblet cells declines.
5. The relative amount of smooth muscle increases.

Respiratory zone structures are defined by the presence of thin-walled alveoli. Alveoli are the sites of gas exchange. They're first seen w/i respiratory bronchioles. There, the alveoli are not adjacent and are separated by a thicker epithelium. Respiratory bronchioles lead into alveolar ducts. In them, the alveoli are adjacent to one another. Alveolar ducts terminate as **alveolar sacs**, blind clusters of alveoli. There are about 300 million alveoli within the lungs.

The walls of the alveoli are made of simple squamous epithelial cells known as **type I alveolar cells**. Cobwebbing the external surface of the alveoli are **pulmonary capillaries**. These capillaries are lined by endothelium. O₂ and CO₂ are exchanged as they pass through both sets of simple squamous epithelia (alveolar and capillary) as well as the basement membrane between the 2. This structure is collectively known as the **respiratory membrane**. Its extreme thinness facilitates the diffusion of O₂ and CO₂. Interspersed amongst the type I alveolar cells are **type II alveolar cells**. These cells function primarily in the production of **surfactant**, a chemical that helps prevent alveolar collapse. Alveoli are connected to one another via **alveolar pores**. These allow pressure to be equalized among alveoli. **Alveolar macrophages (dust cells)** monitor the surface of the alveoli. In addition to capillaries, alveoli are also covered by a network of **elastic fibers** – which assist with normal expiration.

The **lungs** occupy the entire **thoracic cavity** except for the mediastinum. The thoracic cavity is enclosed and bounded:

- Above by the upper ribs and tissues of the neck.
- At the sides by the ribs and intercostal muscles.
- At the back by the ribs and vertebral column.
- In front by the ribs, costal cartilages, and sternum.
- Below by the **diaphragm** (a strong dome-shaped sheet of skeletal muscle with a central tendon).

Each lung is cone-shaped, associated with its own **pleural cavity**, and connected to the mediastinum by bronchial and vascular attachments known as the **root of the lung**. Anterior, lateral, and posterior surfaces hug the ribs and form the **costal surfaces**. Deep

to the clavicle is the **apex**, the narrow superior lung tip. On the medial side of each lung is an indentation known as the **hilum**. **Pulmonary arteries, pulmonary veins, bronchial arteries** (which feed the support tissues (**stroma**) of the lungs), nerves of the **pulmonary plexus**, and lymphatics enter/exit at this point. The left lung is slightly smaller than the right and contains a concavity known as the **cardiac notch**. The left lung has only 2 lobes – **superior** and **inferior** separated by an **oblique fissure**. The right lung has 3 lobes – **superior, middle, and inferior** separated by **oblique** and **horizontal fissures** respectively. The lobes themselves are further divided into **bronchopulmonary segments** (each associated with a segmental bronchus), which are in turned divided into **lobules** (each associated with a single bronchiole).

The **pleurae** are the thin, double-layered serosa that covers each lung. The **parietal pleura** covers the thoracic wall, the superior surface of the diaphragm, and the mediastinum. It continues around the heart and between the lungs. At the hilum, the parietal pleura is continuous w/ the **visceral pleura**, which covers the external surface of the lungs themselves. The pleurae produce pleural fluid which fills the slit-like **pleural cavity** btwn them. Pleural fluid reduces friction and helps the parietal and visceral pleurae adhere to one another.

The basic mechanism of breathing includes 2 phases – **inspiration** and **expiration**. Air movement occurs when a pressure gradient exists between the air within the lung alveoli and the air in the surrounding atmosphere. There are 3 pressures vital for lung function:

1. **Atmospheric pressure** – pressure exerted by the air surrounding the body. Normal value is 760 mmHg.
2. **Intrapulmonary pressure** – pressure exerted by the air within the alveoli. Changes during each cycle of respiration.
3. **Intrapleural pressure** – pressure within the pleural cavity. Changes during each respiratory cycle, but always less than intrapulmonary pressure.

The lungs are naturally elastic and would have a tendency to collapse if there was not an opposing force keeping them open. The basis of the opposing force is provided by the presence of a pressure gradient (**transpulmonary pressure**) between the alveoli and the pleural cavity. Intrapleural pressure is always lower than alveolar pressure. Thus, the air within the alveoli is always “attempting” to leave the alveoli and enter the pleural cavity. This prevents alveolar collapse. If intrapleural pressure equilibrates with alveolar pressure, this gradient is lost and lung collapse can occur. One way the pressure gradient can be lost is if the pleural cavity is opened to the external environment – due to a stab wound perhaps.

The relationship between pressure and volume is given by **Boyle’s Law**, which states that at constant temperature, the pressure of a gas varies inversely with its volume. Thus changes in lung pressure (i.e., the creation of gradients btwn the lungs and the atmosphere) can be achieved by changing lung volume. Changing lung volume is achieved by changing the volume of the thoracic cavity via skeletal muscle contraction.

The following is the sequence of the **quiet inspiratory process**:

1. **Respiratory centers** in the **ventral medulla oblongata** become active.
2. Signals are sent down the **phrenic nerve** to the **diaphragm** and down **intercostal nerves** to the **external intercostal muscles**.
3. Diaphragm and external intercostals contract.
4. Contraction of the diaphragm lengthens the thoracic cavity top to bottom. Contraction of the external intercostals lifts the ribs and sternum increasing the side-to-side and front-to-back dimensions of the thoracic cavity.
5. Volume of the thoracic cavity increases.
6. Lung volume increases.
7. Alveolar pressure decreases. Alveolar pressure is now $<$ atmospheric pressure.
8. Air flows from the atmosphere into the alveoli until alveolar $P =$ atmospheric P .

In **forced inspiration**, other muscles are involved so as to further increase thoracic volume (and further decrease alveolar pressure). Such muscles include the **scalenes** and **sternocleidomastoids** of the neck, the **pectoralis minors** of the chest, and the **erector spinae** of the back.

Quiet expiration is a passive process, (i.e., not powered by skeletal muscle contraction).

1. Phrenic and intercostal nerves cease firing.
2. Diaphragm and external intercostals relax.
3. The thoracic volume decreases.
4. Lung volume decreases.
5. Alveolar pressure increases. Alveolar pressure is now $>$ atmospheric pressure.
6. Air flows from the alveoli into the atmosphere until alveolar $P =$ atmospheric P .

In **forced expiration**, muscles contract in order to further reduce the size of thoracic cavity (and further increase alveolar pressure). Such muscles include the **rectus abdominis**, **transverse abdominis**, **obliques**, and **internal intercostals**.

Airway resistance can sometimes affect airflow. It's normally insignificant due to the relatively large diameters of the air passages, low viscosity of air, and incredible amount of branching. However, during severe allergic reactions histamine causes contraction of bronchiolar smooth muscle. This decreases airway volume and increase airway resistance. During an asthma attack, vigorous bronchoconstriction can also occur. Mucus or accumulations of infectious material can increase airway resistance. Epinephrine causes relaxation of bronchiolar smooth muscle, increasing bronchiole diameter and decreasing airway resistance.

Another complicating factor is **surface tension**. Water molecules line the inner surfaces of the alveoli. These water molecules have a stronger attraction for one another than for the molecules of gas within the alveolar lumen. This high surface tension can lead to alveolar collapse. Collapsed alveoli require large amounts of energy to inflate during inspiration. Luckily, the type II alveolar cells produce the chemical surfactant. It decreases the cohesiveness of the water molecules and thus reduces alveolar surface tension and decreases the likelihood of alveolar collapse.

Compliance refers to the ability of the lungs to expand. The ease with which the lungs can expand facilitates efficient ventilation. Replacement of the elastic lung tissue with inelastic scar tissue as well as reduced surfactant production will decrease lung compliance. The thoracic cage also needs to be compliant as it expands during the inspiratory process. Too much compliance is undesirable since it hinders the ability to exhale.

The amount of air that moves in and out of the lungs in one breath is the **tidal volume**. Any extra air that can be inspired after a tidal inhalation is the **inspiratory reserve volume**. Any extra air that can be expired after a tidal exhalation is the **expiratory reserve volume**. The amount of air remaining in the lungs following max expiration is the **residual volume**.

Inspiratory capacity is the amount of air that can be breathed in after a normal exhalation, i.e., the sum of TV and IRV. **Functional residual capacity** is the amount of air remaining in the lungs after a normal expiration, i.e. the sum of ERV and RV. **Vital capacity** is the total amount of exchangeable air, i.e. the sum of TV, IRV, and ERV. **Total lung capacity** is the sum of all lung volumes.

Not all inspired air is exchanged b/c it does not all reach the alveoli. An example is the air that occupies the conducting zone. B/c that air cannot be exchanged, structures the conducting zone are collectively referred to as the **anatomical dead space**. Any alveoli not involved in exchange (due to collapse or obstruction) comprise the **alveolar dead space**. The combination of anatomical and alveolar dead spaces is known as the **total dead space**.

Non-respiratory air movements include coughing, sneezing, laughing, yawning, and hiccupping.

Air is made up of 79% nitrogen, 20% oxygen, smaller amounts of carbon dioxide and water vapor, and minute amounts of other gases. According to **Dalton's law of partial pressures**, the pressure exerted by atmospheric air is a sum of the pressures exerted by each individual gas in the air. Each gas in a mixture of gases exerts a certain amount of pressure, which is known as the **partial pressure** for that gas. Individual gases tend to move from one place to another based on their partial pressure gradient.

Note that the percentages given above for the gases in the atmosphere will differ a bit from the percentages of gases in alveolar air. Alveolar air will contain a greater percentage of carbon dioxide (since it's continually released from the pulmonary capillaries) as well as a greater percentage of water vapor (since the air was humidified on the way in). It also contains a lower percentage of oxygen (since oxygen is continually leaving the alveolar air space and entering the pulmonary capillaries).

Two important factors (Henry's Law and solubility) affect the movements of gases between alveolar air and pulmonary plasma. According to **Henry's Law**, the amount of gas that will dissolve in a solution is directly related to its partial pressure. Oxygen is

much less soluble in water compared to carbon dioxide thus it will need a greater pressure gradient in order to drive it into solution. Nitrogen on the other hand has a high partial pressure in alveolar air but it is rather insoluble so little tends to dissolve in plasma.

During gas exchange in the lungs the partial pressure of O₂ in the alveoli is 104mmHg. The partial pressure of O₂ in blood entering pulmonary capillaries is 40mmHg. The PO₂ gradient favors flow of O₂ from alveolar air into the pulmonary capillary blood. Meanwhile, the partial pressure of CO₂ in the alveoli is 40mmHg. The partial pressure of CO₂ in blood entering the pulmonary capillaries is 45mmHg. The PCO₂ gradient favors flow of CO₂ from pulmonary capillary blood into the alveolar air.

Gas exchange in the lungs also depends on **ventilation-perfusion coupling** as well as the thickness of the **respiratory membrane**. Ventilation-perfusion coupling refers to how blood is distributed to capillaries that surround alveoli rich in oxygen. This maximizes the efficient exchange of gases. It works b/c high alveolar PO₂ stimulates local pulmonary arterioles to dilate. And as previously mentioned, the extreme thinness of the respiratory membrane and its humongous surface area work in tandem to facilitate the diffusion of gases.

At the systemic tissues, the situation is reversed. Arterial blood PO₂ is 104mmHg while tissue PO₂ is less than 40mmHg. The PO₂ gradient favors flow of O₂ from the systemic capillary blood into the interstitial fluid and tissue cells. Meanwhile, arterial blood PCO₂ is 40mmHg while tissue PCO₂ is greater than 45mmHg. The PCO₂ gradient favors flow of CO₂ from interstitial fluid and tissue cells into systemic capillary blood.

O₂ is carried by blood in 2 ways. 1.5% of the O₂ is simply dissolved in plasma. The other 98.5% is bound to **hemoglobin** within red blood cells.

Each Hb molecule can combine with up to 4 oxygen molecules. Hemoglobin with bound O₂ is **oxyhemoglobin**. Hemoglobin w/o bound O₂ is **reduced hemoglobin**. The loading and unloading of O₂ by hemoglobin is given by a single reversible equation: $\text{HHb} + \text{O}_2 \leftrightarrow \text{HbO}_2 + \text{H}^+$. In the lungs (highPO₂), the reaction runs from left to right. In the tissues (low PO₂), the reaction runs from right to left. When Hb has 4 O₂ molecules bound to it, it's **saturated**. When Hb has less than 4 O₂ molecules bound to it, it's **unsaturated**. In the lungs (PO₂ is 104mmHg), Hb is fully saturated. In the tissues (PO₂ is 40mmHg), Hb is 75% saturated, meaning that, on average, each Hb molecule has 3 molecules of O₂ bound to it. Thus, substantial amounts of O₂ are still available in the venous blood. This provides a **venous reserve** for use during increased activity. During aerobic respiration, working muscle cells produce CO₂, heat, and acid. These factors decrease the affinity that Hb has for O₂, making Hb more likely to release O₂ to these working cells. Both a rise in PCO₂ and a drop in pH substantially weaken the bond btwn Hb and O₂. This is known as the **Bohr effect**.

CO₂ is transported w/i blood in 3 ways. About 10% is dissolved in plasma. Another 20% is bound to hemoglobin. The equation for this combination is: $\text{Hb} + \text{CO}_2 \leftrightarrow$

HbCO₂. HbCO₂ is known as **carbaminohemoglobin**. CO₂ binds to Hb in a different place than O₂. (However note that Hb is better able to bind CO₂ when the Hb is not saturated with O₂ – this is known as **Haldane effect**). The remaining 70% is transported as part of the **bicarbonate ion** in plasma.

When CO₂ diffuses out of the tissue fluid, it enters the systemic capillary plasma and then the RBC. Within the RBC, CO₂ combines with water to form **carbonic acid**, which dissociates into a **bicarbonate ion** and a **hydrogen ion**. The equation is: **CO₂ + H₂O ↔ H₂CO₃ ↔ HCO₃⁻ + H⁺**. This reaction is catalyzed by the enzyme **carbonic anhydrase**. Once bicarbonate is formed it diffuses out of the RBC into the plasma. As this occurs, a **chloride ion** diffuses from the plasma into the RBC. This maintains charge balance and is known as the **chloride shift**. At the pulmonary capillaries, the above events reverse themselves.

The primary control center for respiration is a cluster of neurons in the medulla oblongata known as the **ventral respiratory group (VRG)**. It contains both **inspiratory neurons** and **expiratory neurons**. When the inspiratory neurons fire, signals travel down the phrenic and intercostal nerves and excite the diaphragm and external intercostals – resulting in inspiration. When the expiratory neurons fire, the output to the diaphragm and external intercostals ceases and expiration occurs. The on/off cycle of both these types of neurons creates the basic respiratory rhythm – known as **eupnea**.

There is also a **dorsal respiratory group (DRG)**, which helps to integrate information from peripheral chemoreceptors and stretch receptors. It then inputs this info to the VRG. In the pons, we find the **pontine respiratory group**, which helps modify, breathing rhythm during sleep, talking, and exercise.

The primary factors that influence respiratory rate are the contents of the plasma and the cerebrospinal fluid. The main respiratory stimuli in order of importance are: **CSF pH**; **plasma PCO₂** and **pH**; and the **plasma PO₂**. **Central chemoreceptors** on the medulla measure the [H⁺] of the CSF. **Peripheral chemoreceptors** (located primarily in the aortic arch and carotid sinus) measure the PCO₂, [H⁺], and PO₂ of the plasma.

When plasma CO₂ levels rise, CSF CO₂ levels rise (since CO₂ can easily diffuse thru the blood-brain barrier and enter the CSF from the plasma). Within the CSF, CO₂ combines with H₂O to form HCO₃⁻ and H⁺. Thus, as plasma CO₂ levels rise, CSF pH will decrease. A drop in CSF pH can be quite damaging. Luckily, the medullary chemoreceptors sense the low pH and initiate an ↑ in respiratory rate and depth to rid the body of excess CO₂. The lowering in pH of the CSF as caused by the rise of CSF PCO₂ as caused by the rise of plasma PCO₂ is the most powerful respiratory stimulus.

When plasma PCO₂ reaches its threshold or when plasma pH drops to its threshold, the peripheral chemoreceptors are activated and they signal the medulla (via the **vagus** and **glossopharyngeal nerves**) to increase respiratory rate and depth. Recall how CO₂ combines with H₂O to form bicarbonate and a hydrogen ion. This is why ↑ plasma CO₂ results in ↑ plasma H⁺ and ↓ plasma pH.

Arterial PO_2 must drop substantially (i.e., to below 60mmHg) before the chemoreceptors sensitive to PO_2 play a role in activating the respiratory centers. In people who chronically retain CO_2 , (perhaps due to **emphysema** or chronic bronchitis) the peripheral PCO_2 receptors become unresponsive. In such individuals, arterial PO_2 levels play a significant role in respiration regulation.

Factors outside the brainstem also influence respiratory rate and depth. The presence of irritants in the respiratory tract can lead to coughing and sneezing as well as cause other changes in rate and depth. The **inflation reflex** describes another factor. As forced inhalation proceeds, the lungs stretch. Excess stimulation of lung stretch receptors inhibits the medullary inspiratory neurons and activates medullary expiratory neurons. The **hypothalamus** exerts effects as well. An example is the changes in respiratory rate and depth associated with changes in body T° . In general, as body $T^\circ \uparrow$, respiratory rate and depth \uparrow ; and as body $T^\circ \downarrow$, respiratory rate and depth \downarrow . Changes in BP affect respiration rate and depth. When BP falls, the respiratory rate increases. When BP rises, the respiratory rate declines. The **cerebral cortex** also influences respiratory rate, e.g., our ability to hold our breath (for a limited time at least). Respiratory rhythm is of course altered by laughing, yawning, crying, speech, hiccupping, etc.

It should be noted that the respiratory system can both cause and correct disturbances in plasma pH. The respiratory system can cause plasma pH disturbances in 2 ways. During **hyperventilation**, plasma CO_2 drops. This causes a decrease in plasma H^+ and thus, an increase in plasma pH. If plasma pH rises above normal levels, it is known as **plasma alkalosis**. In this case, we call it **respiratory alkalosis**. During **hypoventilation**, plasma CO_2 increases. This causes an increase in plasma H^+ and thus, a decrease in plasma pH. If plasma pH drops below normal levels, it is known as **plasma acidosis**. In this case we call it **respiratory acidosis**.

Plasma pH disturbances are not always respiratory in origin. Any alkalosis not caused by respiratory malfunctions is referred to as **metabolic alkalosis**. Causes of metabolic alkalosis include:

1. Vomiting – due to the loss of gastric HCl.
2. Ingestion of excessive antacids (e.g., sodium bicarbonate).
3. Constipation – decreased loss of HCO_3^- in feces.

In response to metabolic alkalosis, respiratory rate and depth will decrease. This will increase plasma CO_2 levels and decrease plasma pH.

Any acidosis not caused by respiratory malfunctions is referred to as **metabolic acidosis**. Causes of metabolic acidosis include:

1. Severe diarrhea – excess HCO_3^- loss in feces.
2. Renal disease – failure of kidneys to secrete acids in urine.
3. Excess alcohol ingestion. (Byproducts of alcohol metabolism are acidic.)
4. Starvation – when the body begins to break down fat and muscle protein reserves for energy, acidic metabolites (**ketone bodies**) are produced.

5. Untreated **diabetes mellitus** – fats are broken down and ketone bodies are produced.

In response to metabolic acidosis, respiratory rate and depth will increase. This will decrease plasma CO₂ levels and increase plasma pH.