Written and Edited by Z

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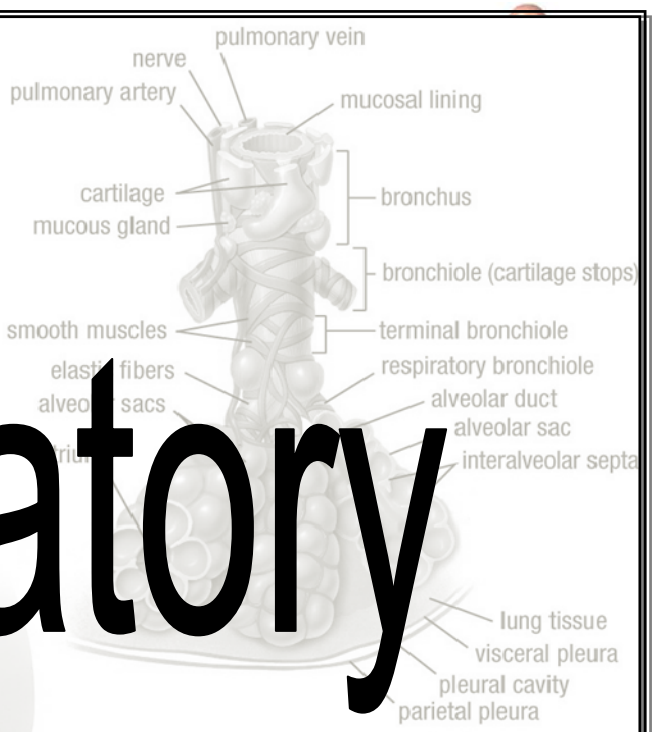
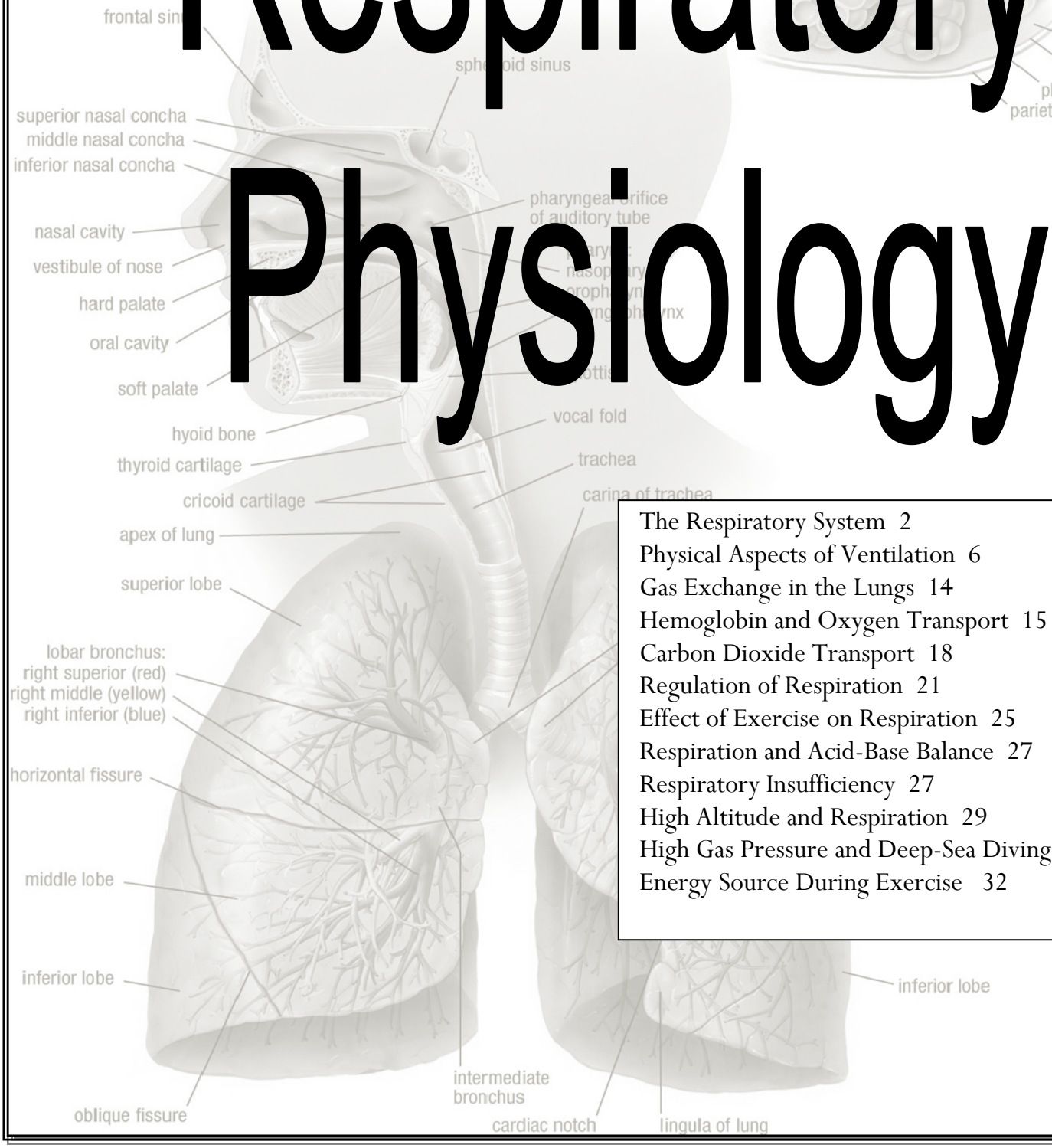
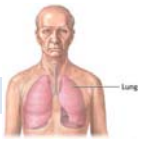
Respiratory Physiology







RESPIRATORY PHYSIOLOGY

Respiration has two DEFINITIONS:

1) **External respiration**, which includes:
   a. *Ventilation*: is the mechanical process that moves air into and out of the lungs (breathing).
   b. *Exchange of gases* (O_2 and CO_2).

⇨ External respiration occurs on the level of the lungs.

2) **Internal respiration**: is the utilization (use) of O_2 by cells and production of CO_2 by metabolism.

⇨ Internal respiration occurs on the level of the cells.

STRUCTURAL AND FUNCTIONAL RELATIONSHIPS OF THE LUNGS

The lung consists of the AIRWAY TREE:

⇨ Trachea ➔ bronchi ➡ segmental bronchi ➡ terminal bronchioles ➔ respiratory bronchioles ➔ alveolar ducts ➔ alveolar sacs.

➢ Each bronchus gives (1) *narrower*, (2) *shorter*, and (3) *more numerous* branches as it penetrate the lung.

The respiratory system is divided into two FUNCTIONAL ZONES:

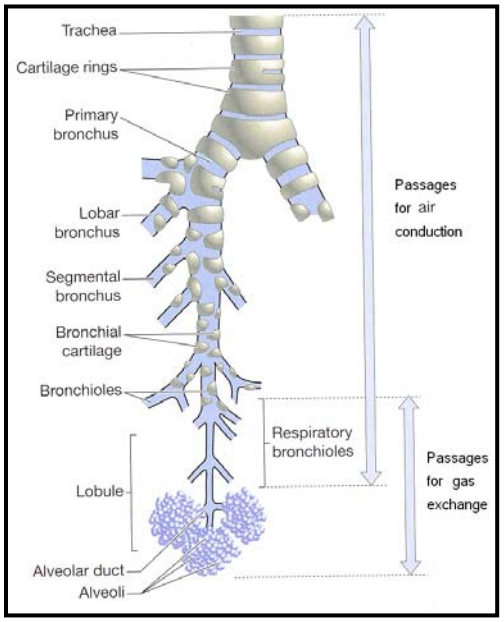
A. **Conducting zone** (first 16 divisions): conducts the air to the lungs, and has three important functions:
   1. *Warm & humidify* the inspired air (air reaches the respiratory zone at body temperature ~ 37ᵁ C).
   2. *Conduct air* to the deeper parts of the lung.
   3. *Filtration & cleaning* (mucus and cilia remove dust, foreign bodies, and harmful gases from the lungs).

➢ The conducting zone constitutes the airway passages from the nose down to the terminal bronchioles.

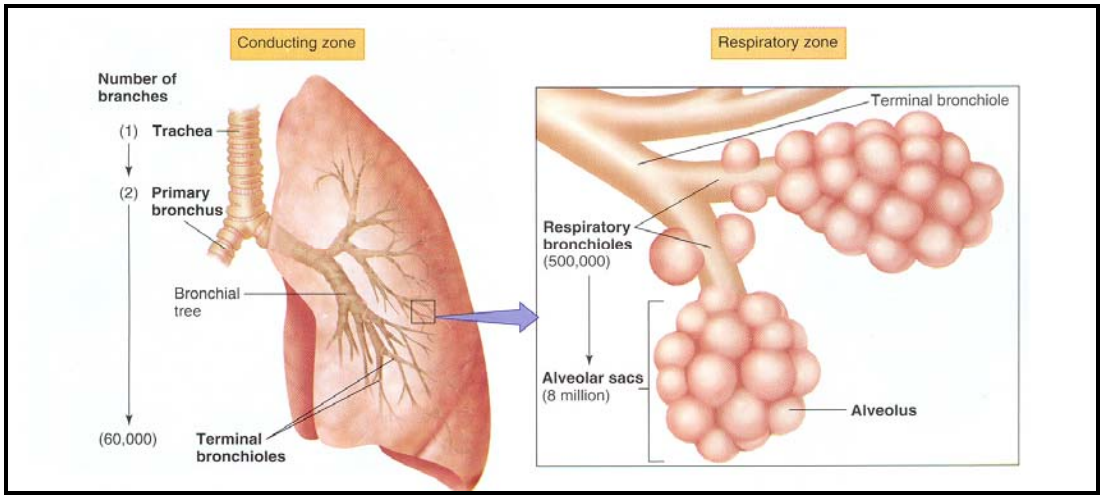
✺ **Note**: No gas exchange occurs in the conducting zone.

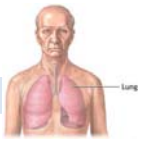
B. **Respiratory zone** (last 7 divisions): it is the only part of the airway passage involved in gas exchange.

➢ The respiratory zone constitutes of the respiratory bronchioles, alveolar ducts, and alveolar sacs.



✺ **Note**: The respiratory zone receives most of the blood from the cardiac output (C.O.).





The lung is supplied by two separate CIRCULATIONS:

I. **Bronchial circulation**: provides nutrients and oxygen for the *conducting airways* and *lung tissue*.

- Originates from the **descending aorta** and its deoxygenated blood is drained mostly into the left atrium via the **pulmonary veins** (two-thirds) and it also drains into the azygos veins (one-third).
- It is part of the systemic circulation and receives **1-2%** of the C.O.

II. **Pulmonary circulation**: supplies *respiratory zone* with deoxygenated blood for gas exchange with alveoli.

- It receives *all* of the C.O. = **5 L** of blood ⇨ therefore, blood flow is very high.
- It is a **low-pressure** (**25/10 mmHg**), low-resistance system.

Most important aspect in respiration is that the respiratory pathways remain **PATENT** (open):

- The **trachea** is kept open by 16-20 **C**-shaped cartilages that constitute $^5/_6$ of its entire surface area with smooth muscle constituting the rest.
- There are no cartilages in and after the **terminal bronchioles**, there is only smooth muscle.

✺ **Note**: Contraction of the smooth muscle in terminal bronchioles and respiratory bronchioles obstructs breathing, such as in asthma.

Factors affecting the smooth muscle of the respiratory pathway:

	Bronchi	Mucus Secretion
① *Sympathetic* (epinephrine & norepinephrine) ⇨ β_2 receptors	Dilates	Decrease
② *Parasympathetic* (acetylcholine)	Constricts	Increase
③ *Histamine*, ④ *Slow reacting substance of anaphylaxis* (both released by mast cells in lung during an allergic reaction, e.g., allergic asthma)	Constricts	Increase

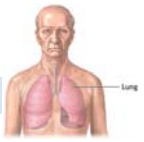
FUNCTIONS OF THE RESPIRATORY PATHWAYS

The main function of the respiratory system is to facilitate the exchange of O_2 and CO_2 between the air and blood, but it also has many other nonrespiratory functions:

A. Body defense:

- **Nose**: contains blood vessels, mucus, and hair. Due to turbulent air flow in the nasal cavity caused by the conchae, the nasal cavity performs three air conditioning functions:
  1) *Warming*: inspired air hits many blood vessels ⇨ blood warms the air to body temperature.
  2) *Humidifying*: the inspired air hits the mucus in the nose ⇨ the mucus humidifies the air.
  3) *Filtration*:
     - Any particle larger than 10 µm ⇨ trapped by hair in the nose.
     - Any particle from 4-6 µm ⇨ will stick to the mucus of the nose.
- **Cilia**: lines the entire surface of the respiratory passages and function in moving the mucus secreted by cells and the particles stuck to it into the pharynx to be either swallowed or expectorated (coughed out).
  - Cilia above pharynx: contract downward. Cilia below pharynx ⇨ contract upwards.
  - There are about 200 cilia per cell that beat continually at a rate of 10-20 times per second.
  - **Note:** Cilia above pharynx ⇨ contract down
- **Macrophages**: are a protective function in the alveoli against any particle that enters the lung.
  - Particles < 4µm in size can enter into alveoli, but are phagocytosed by *alveolar macrophages*.

✺ **Note**: Smoking can inhibit macrophages and the movement of cilia and may cause **bronchitis**.



B. *Metabolic or endocrine functions of the lungs*:

1) **Production of *surfactant***: a lipoprotein secreted into the alveoli by **type II alveolar cells** to lower surface tension, and consists mainly of phospholipids as well as hydrophobic proteins and ions (Ca^{++}).
   - Water tension in the alveolus tries to collapse the alveolus by acting inward.
   - Surfactant becomes scattered between the air and water layer of the alveolus and works to decrease the surface tension caused by this thin layer of water that is normally present in the alveolus.
   - Surfactant functions to (a) *reduce the surface tension*, (b) *prevent collapse of the alveoli*, and (c) *make subsequent inspiration* (expansion of the lung) *easier* by keeping the alveoli open.

- In fetuses, **surfactant** is synthesized at 34 weeks of a 40 week pregnancy. Therefore, premature babies with a deficiency in surfactant will have **collapsed alveoli** ⇨ a condition called **infant respiratory distress syndrome** (IRDS). The high surface tension in these infants causes pulmonary edema and ***atelectasis*** (alveolar collapse).
  - Mothers with fetuses at risk can be given corticosteroids to accelerate the maturation of their fetus's lungs (to produce an adequate amount of surfactant).
- In adults, patients recovering from anesthesia and patients who have undergone abdominal or thoracic surgery and often find it too painful to breath deeply, have shallow breaths. This can result in poor surfactant spreading, causing part of their lungs to become actelectatic (collapsed).
  - These patients are often encouraged to breath deeply to enhance the spreading of surfactant.

2) **Secretion of *converting enzyme***: the lung secrets *angiotensin-converting enzyme* (ACE) that converses **angiotensin I → angiotensin II** which is a very powerful *vasoconstrictor* and acts on the kidneys to *decrease the excretion of both salt and water* thereby increasing the blood pressure.
   ⇨ Some drugs inhibit this converting enzyme, and are called ***ACE inhibitors***.

3) **Inactivation of organic compounds**:
   ① Prostaglandins. ② Serotonin (also called 5-hydroxytryptamine).
   ③ Epinephrine. ④ Kallikrein (e.g. bradykinin up to 80%).

4) **Acid-base balance of blood**: regulates H^+ concentration.

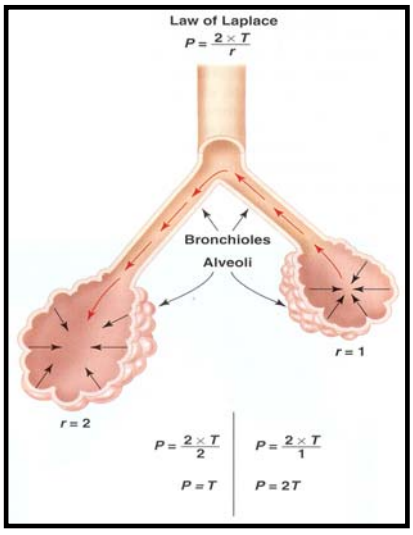
5) **Acts as blood reservoir** in case of hemorrhagic shock (contains 10% of C.O. in pulmonary circulation).

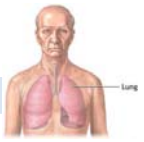
C. *Vocalization*: it involves:
   - *Phonation*: by the vocal cords.
   - *Articulation*: include the lips, tongue, and soft palate.
   - *Resonance*: include the mouth, nose, nasal sinuses, and pharynx.

LAW OF LAPLACE

- The law of Laplace's explains the relationship between pressure (*P*), surface tension (*T*), and radius (*r*) of an alveoli in the lung, where: ***P = 2T/r***
- *According to the law of Laplace*:
  - The pressure created by surface tension is **greater** in *smaller alveoli* with a decreased radius than in larger alveoli with an increased radius.
  - During deficiency of surfactant when the tension is the same in small and large alveoli, *the smaller alveoli will collapse first* because of a higher pressure due to their small radius.

☞ **In short**: ↓ Radius ⇨ ↑ Pressure ⇨ ↑ Tension.





MECHANICS OF BREATHING

Muscles of Inspiration:

- *Quiet* (unforced) *Inspiration*:
  - The **diaphragm** is the main muscle of inspiration; it moves 1-2 cm downward, increasing the thoracic volume which decreases the thoracic pressure causing air to enter the lungs.
- *Deep* (forced) *Inspiration*:
  - ① **Diaphragm**: In deep inspiration, the diaphragm may move 10-12 cm downward.
  - ② **Accessory muscles**:
    - ❶ **External intercostal muscles**: Raises the anterior end of the rib cage when taking a deep breath.
    - ❷ **Scaleni muscles**: Elevates upper rib cage during deep and heavy breathing, e.g. exhaustive exercise.
    - ❸ **Sternocleidomastoid muscles**: Also elevates the upper rib cage during deep and heavy breathing.
- **Note**: Both quiet and deep inspirations are *active processes* that require contraction of respiratory muscles.

- *Obesity*, *pregnancy*, and *tight clothing around the abdominal wall* can impede the effectiveness of the **diaphragm** in enlarging the thoracic cage.
- Damage to the **phrenic nerves** can lead to *paralyses* of the **diaphragm**. When a phrenic nerve is damaged, that portion of the diaphragm ***moves up rather than down during inspiration***.

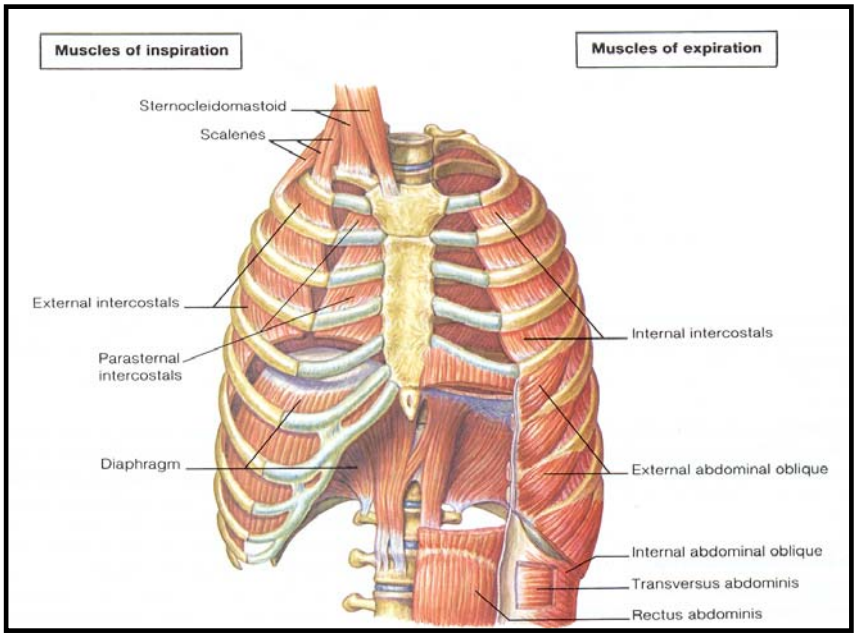
Muscles of Expiration:

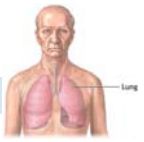
- *Quiet* (unforced) *Expiration*:
  - Quiet expiration is a *passive process*. The diaphragm relaxes, the rib cage drops, and the thorax and lung recoil as a result of their **elastic tension**. The decrease in lung volume raises the pressure in the alveoli and pushes the air out.
- *Deep* (forced) *Expiration*:

  ① **Abdominal muscles**: Contraction of the abdominal muscles pushes the diaphragm into the chest.

  ② **Internal intercostal muscles**: Pull the rib cage down, reducing the thoracic volume.

- **Note**: Deep expiration is an *active process* that requires the contraction of accessory muscles and is necessary for such functions as coughing, straining, vomiting, and defecating.





PHYSICAL ASPECTS OF VENTILATION

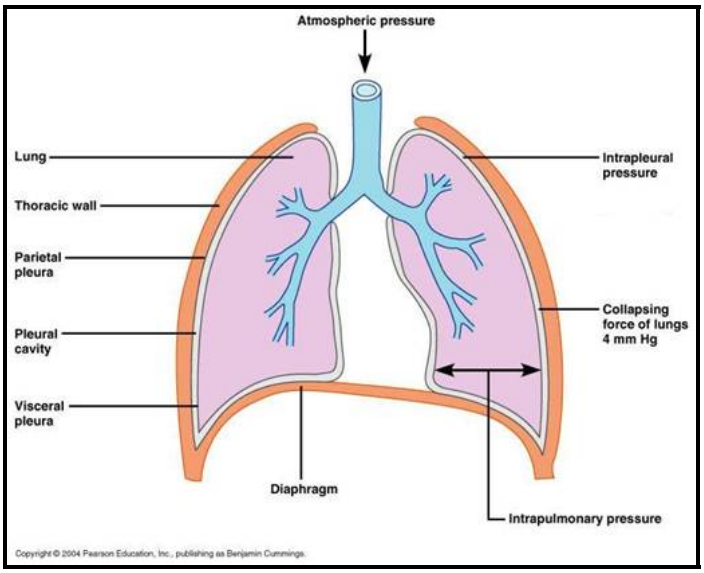
- ***Ventilation***: The entry and exit of air from the lungs as a result of a difference in pressure caused by changes in lung volume.

- ***Alveolar (intrapulmonary) Pressure***: The pressure of the air inside the lung alveoli.
  - During inspiration, the alveolar pressure becomes slightly negative (–3 cmH_2O below atm pressure).
  - During expiration, the alveolar pressure becomes slightly positive (+3 cmH_2O above atm pressure).
  - At the end of expiration, when there is no air entering or leaving the lungs, the pressure inside the lung is zero (equal to atmospheric pressure) because the alveoli are in direct contact with the air through the nose.

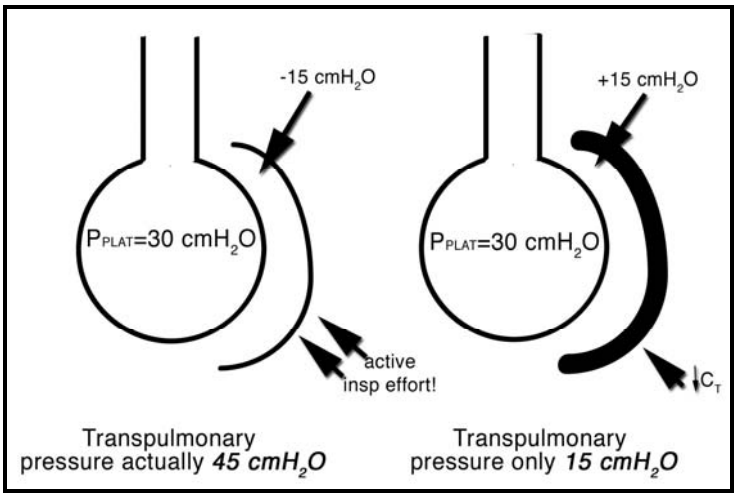
- ***Intrapleural Pressure***: The pressure of the fluid in the intrapleural space between the lung and chest wall.
  - The *intrapleural space* contains a thin film of fluid between the lung and chest wall that *reduces friction* and *lubricates the movement* of the lung inside the thoracic cavity.
  - During inspiration, the intrapleural pressure is lower (–6 cm H_2O below atm pressure; **more negative**).
  - During expiration, the intrapleural pressure is higher (–3 cm H_2O below atm pressure, **less negative**).
  - **Note**: The intrapleural pressure is normally lower than the intrapulmonary space during both inspiration and expiration, in other words, it is always negative.

- Intrapleural pressure can decrease to –30 mmHg during deep inspiration.
- During forced expiration, the intrapleural pressure can increase to +100 mmHg. This can be achieved by the **Valsalva maneuver**; forced expiration against a closed glottis ⇨ causes an increase in blood pressure in the chest veins ⇨ ↑ pressure in right atrium ⇨ Prevents venous return ⇨ can affect coronary circulation and cause a myocardial infarction in people with heart problems.
- Valsalva maneuver occurs during:- Heavy weight lifting, Straining, Labor or defecation.

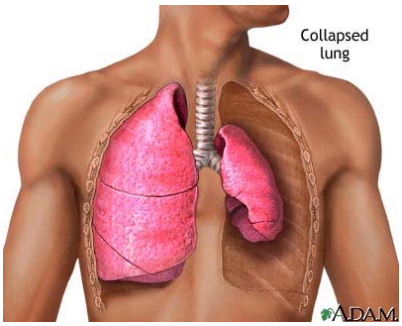
- ***Transpulmonary Pressure***: The pressure difference between alveolar pressure and intrapleural pressure.
  - It is a measure of the elastic forces in the lungs that tend to collapse the lungs at each instant of respiration, called the ***recoil pressure***.
  - During inspiration, transpulmonary pressure = (–3) – (–6) = +3.
  - During expiration, transpulmonary pressure = (+3) – (–3) = +6.
  - Since the pressure within the lungs (alveolar pressure) is greater than the pressure outside the lungs (intrapleural pressure), the difference in pressure (transpulmonary pressure) *keeps the lungs expanded* against the chest wall and *prevents it from collapsing*.
  - **Note**: The transpulmonary pressure = alveolar pressure – intrapleural pressure
    ⇨ Therefore, the *transpulmonary pressure is* **always positive**.
  - **Note**: If the transpulmonary pressure reaches zero or becomes negative (as a result of an open chest wound, for example), the lungs will collapse. No breath sound is present in case of lung collapse on that side.
    - The other lung doesn't collapse as it is protected by mediastinal membrane.



a. Intrapulmonary and Intrapleural pressure. b. Transpulmonary pressure.



- When air enters the intrapleural space, a condition called **pneumothorax** (as a result of an open chest wound, for example), the intrapleural pressure becomes equal to the atmospheric pressure and the lung can no longer expand. And due to the elastic nature of the lung, the lung collapses away from the chest wall, a condition called ***atelectasis***. Fortunately, a pneumothorax usually causes only one lung to collapse, since each lung is contained in a separate pleural compartment.



- ***Transairway pressure***: The pressure difference between the inside and outside of the airways "*in* minus *out*".
  - *Transairway pressure is* **always positive**, and is important in keeping the airways open during forced expiration.

Resistance to Airflow

(1) Determined mainly by **airway diameter**.

(2) Is ***greatest*** in the **largest** and **medium airways** (due to presence of **cartilage**).

(3) At low lung volume, airways are compressed ⇨ ↑ airway resistance.
  - **Airway resistance** is *inversely* related to **lung volume**.

(4) **Small** and **terminal airways** are ***very low in resistance***.
  - So, during expiration ⇨ ↑ resistance.
  - During inspiration ⇨ ↓ resistance (stretch of bronchi).

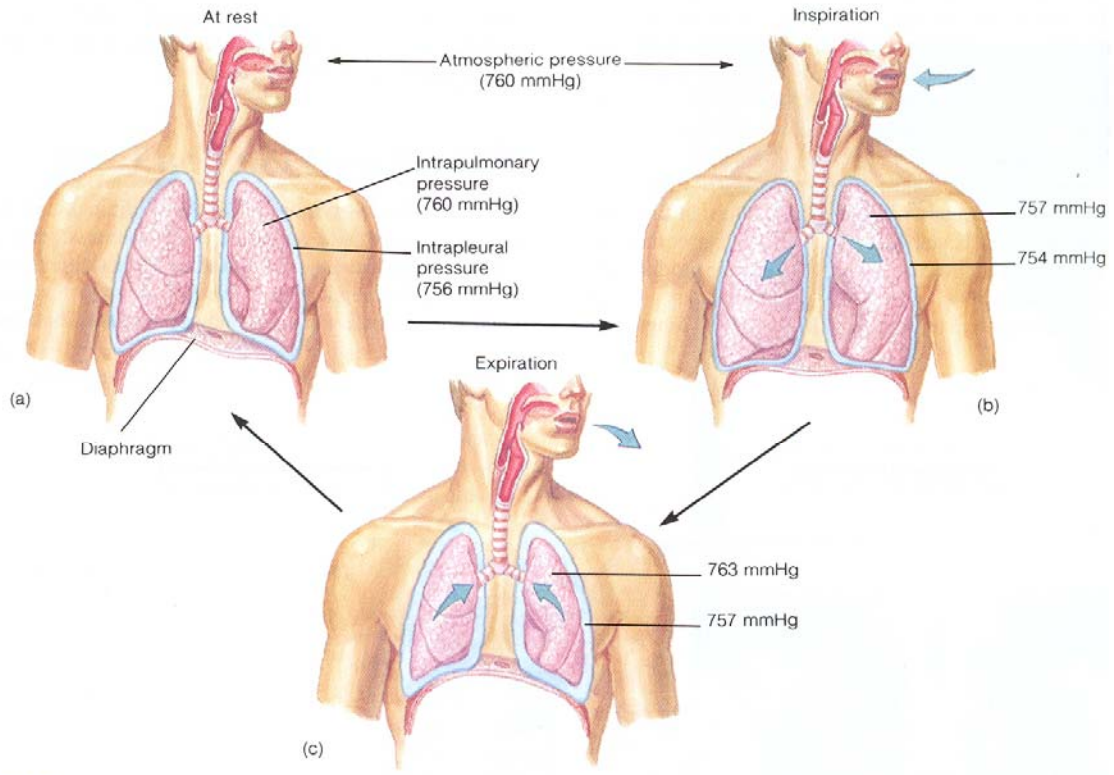


Figure 16.15 **The mechanics of pulmonary ventilation.** Pressures (at sea level) are shown *(a)* before inspiration, *(b)* during inspiration, and *(c)* during expiration. During inspiration, the intrapulmonary pressure is lower than the atmospheric pressure, and during expiration it is greater than the atmospheric pressure.

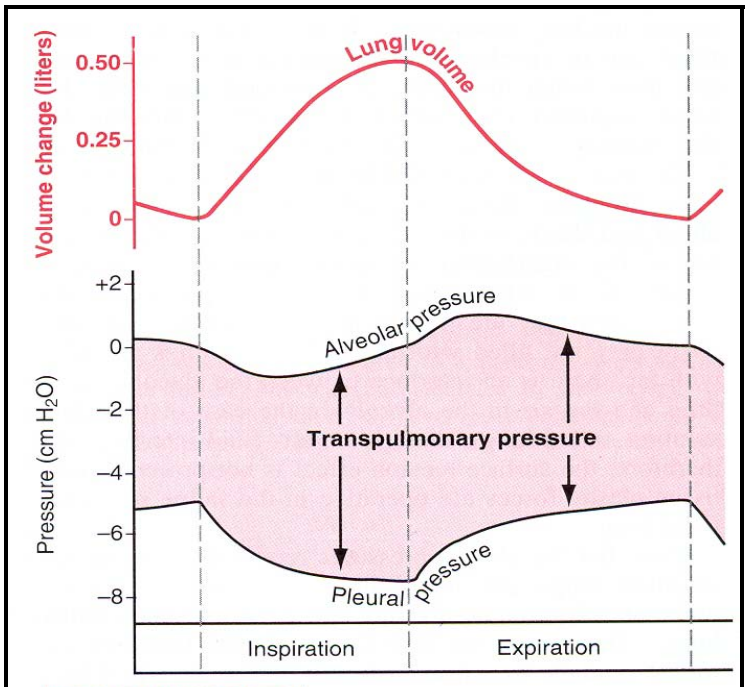


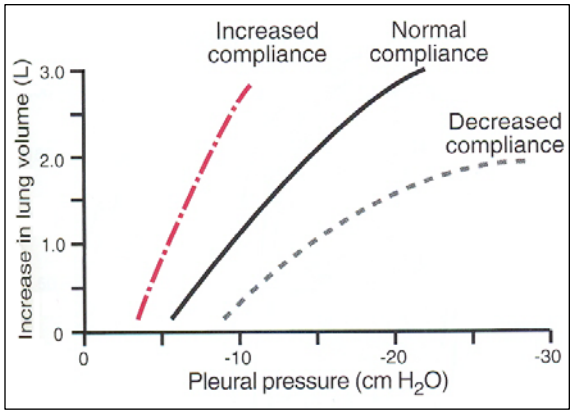
FIGURE 37–2

Changes in lung volume, alveolar pressure, pleural pressure, and transpulmonary pressure during normal breathing.

Physical Properties of the Lungs:

1) **Compliance**: Is the lung's ability to be expanded (stretched) under pressure.

- **Lung compliance** can be defined as the change in lung volume per change in transpulmonary pressure, expressed symbolically as •V/•P, and normally equals **0.2 L/cm H_2O**.



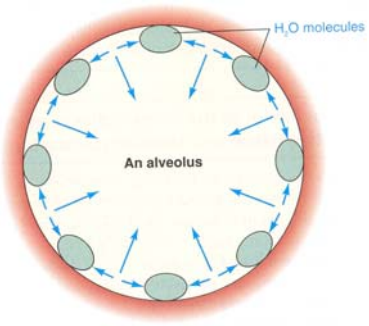
- *Factors that **decrease** lung compliance*:
  - **A. ↓ Lung volume**
    - ① *Pulmonary fibrosis*.
    - ② *Pulmonary edema*.
    - ③ *Deficiency of surfactant*.
    - ④ *Pressure consolidation*.
    - ⑤↑*Intra-abdominal pressure*.
  - **B. Obesity**
  - **C. Constrictive bandages (or tight clothings)**
  - **D. Pregnancy**
- *Factors that **increase** lung compliance*:
  - ❶ *Emphysema*: Increased compliance due to over dispensability of the lung during chronic coughing. (The lung elastic tissue is over stretched because of tissue damage, so there is no recoil)
  - ❷ *Aging*.

2) **Elasticity**: Refers to tendency of the lung to recoil back to its initial size after being stretched.

- Because of the lungs' high content of elastic proteins, they are very elastic and resist distention.
- Since lungs are normally stuck to the chest wall, they are always in a state of **elastic tension**. This tension *increases* during **inspiration** when lungs are stretched and is *reduced* by **elastic recoil** during **expiration**.

3) **Surface Tension**: Is a result of the attraction forces between the water molecules found in the thin film of fluid normally present in alveoli.

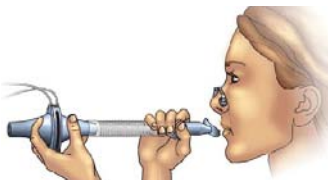
- **Surfactant** acts to decrease surface tension in alveoli, as mentioned earlier, and any deficiency in surfactant will cause an increase in surface tension.



✺ **Note**: Both *elastic resistance* and *surface tension* resist distension (stretching) of the lungs, and an increase in either causes a decrease in lung compliance.

Pulmonary Function Tests

❑ Pulmonary function may be assessed clinically by means of a technique known as *spirometry*.



Lung Volumes

There are **four lung volumes**, which, when added together, equal the **maximum volume** to which the lungs can be expanded:

1) ***Tidal Volume*** **(500 ml)**: V_T

- The volume of air inspired or expired in a normal (unforced) breath.

2) ***Inspiratory Reserve Volume*** (**3000 ml**): IRV
- The maximum volume of air that can be inspired during forced inspiration over and above the tidal volume.

3) ***Expiratory Reserve Volume*** (**1100 ml**): ERV
- The maximum volume of air that can be expired during forced expiration in addition to the tidal volume.

4) ***Residual Volume*** (**1200 ml**): RV
- The volume of air remaining in the lungs after a maximum expiration, because alveoli do not collapse.
- *Importance of RV:*
  - ① It makes the inspiration ***easier***.
  - ② It maintains the ***continuity of gas exchange*** between breaths, especially when holding the breath.

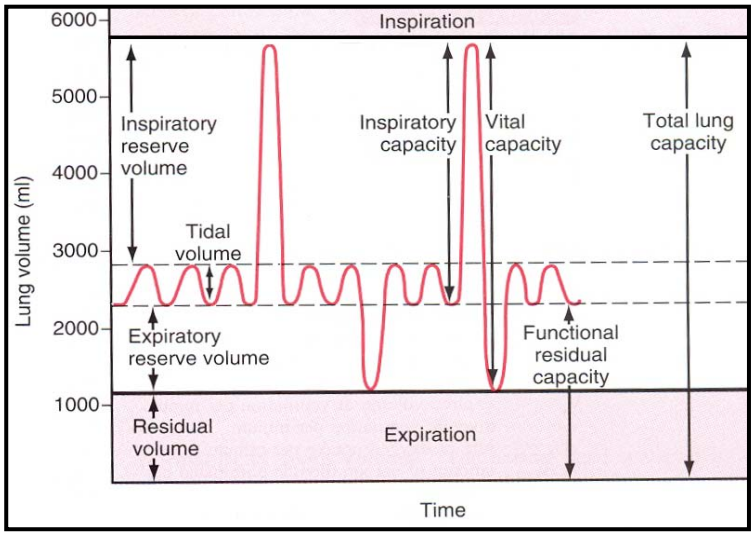
Lung Capacities

A lung capacity is equal to the **sum of two or more lung volumes**. There are **four lung capacities**:

1) ***Inspiratory Capacity*** (**3500 ml**): IC
- The maximum amount of air that can be inspired after a normal tidal expiration.
  - $IC = V_T + IRV$

2) ***Functional Residual Capacity*** (**2300 ml**): FRC
- The amount of air remaining in the lungs after a normal tidal expiration.
  - $FRC = ERV + RV$

3) ***Vital Capacity*** (**4600 ml**): VC (It used in clinical diagnosis.)
- The maximum amount of air that can be expired after a maximum inspiration.
  - $VC = IRV + V_T + ERV$
  - $VC = IC + ERV$

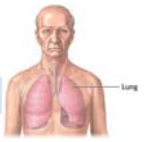


Note: When expiration is performed as rapidly and as forcibly as possible into a spirometer, this volume is called **FORCED VITAL CAPACITY** (FVC) and is about **4600 ml**. To measure FVC, the individual inspires maximally and then exhales into the spirometer as forcibly, rapidly, and completely as possible. Remember, that vital capacity and forced vital capacity are the same volume.

4) ***Total Lung Capacity*** (**5800 ml**): TLC
- The total amount of air in the lungs after a maximum inspiration.
  - $TLC = VC + RV$
  - $TLC = IC + FRC$

Note: Total lung capacity varies from person to person, and is affected by sex, height, and weight.

- Because the lung cannot be completely expired following forced expiration, neither **RV** nor **FRC** can be measured directly by simple spirometry. Instead, they are measured indirectly using a dilution technique involving helium, an inert and relatively insoluble gas that is not readily taken up by the blood in the lungs.
- In woman, all of the lung volumes are less than men by 15-25%.



DEAD SPACE VOLUME

- Not all of the inspired air reaches the alveoli with each breath, some air remains in the conducting airways and does not undergo gas exchange; this volume of wasted air is known as **dead space volume** (V_D).

1) ***Anatomical Dead Space*** (**150 ml**):
   - ◈ Comprises the wasted air in the conducting zone of the respiratory system – nose, mouth, larynx, trachea, bronchi, and bronchioles – where no gas exchange occurs.
   - ➢ Each 500 ml of air inhaled, about **150 ml** remain in conducting airways and are not used in gas exchange.

2) ***Alveolar Dead Space*** (**zero**):
   - ◈ Any air that reaches the alveoli and does not participate in gas exchange, due to *reduced* or *obstructive blood flow* in the alveoli or if there is *alveolar air in excess of that needed* to maintain normal gas exchange, constitutes **alveolar dead space**.
   - ➢ Under normal conditions, alveolar dead space equals **zero** and only occurs when there is an imbalance between alveolar air and alveolar blood flow due to any obstruction in either.

3) ***Physiological Dead Space Volume***:
   - ◈ Physiological V_D is the sum of the *anatomical* and *alveolar dead space* volume.
   - ➢ In normal individuals, physiological V_D is approximately the same as anatomical dead space.

RESPIRATORY MINUTE VOLUME (6 L/min)

- The respiratory minute volume (RMV) is the total amount of new air moved into the respiratory passages per minute, irrelevant of gas exchange.
  - ◈ The respiratory minute volume is equal to the tidal volume times the respiratory rate (RMV = $V_T \times RR$).
  - ➢ The normal tidal volume is about 500 ml, and the normal respiratory rate is about 12 breaths per minute. Therefore, the *minute respiratory volume averages about* ***6 L/min***.

ALVEOLAR VENTILATION (4200 ml/min)

- Alveolar ventilation (AV) is the volume of new air entering the alveoli and gas exchange areas per minute.
  - ◈ Alveolar ventilation is equal to the tidal volume, without the dead space volume, times the respiratory rate.
  - ➢ **AV** = (V_T − V_D) × RR = (500 − 150) × 12 = **4200 ml/min** (wasted air equals about 1800 ml/min).

COMPARISON

- Rapid shallow breaths ***decrease*** the **tidal volume** and consequently ventilation and gas exchange.
- Rapid shallow breathing is more serious than gasping, as it ***decreases*** the **AV** more.

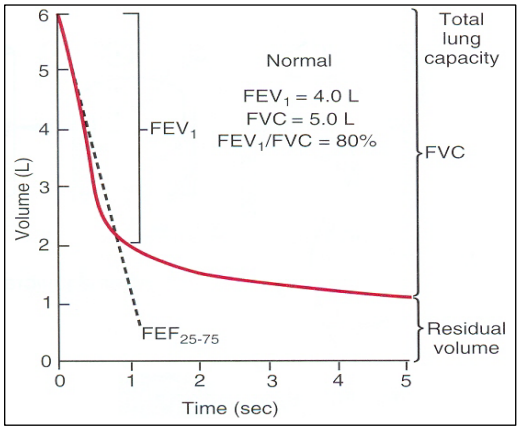
V_T	RR	RMV	AV
500 ml	12/min	6 L/min	**4.2 L/min**
150 ml	40/min	6 L/min	**Zero**
1,000 ml	6/min	6 L/min	**5.1 L/min**
250 ml	24/min	6 L/min	**2.4 L/min**

❁ ***Note****: Tidal volume (V_T), Respiratory Rate (RR), Respiratory Minute Volume (RMV), Alveolar Volume (AV), Dead Space Volume (V_D), not written, is always approximately 150 ml.*

- If **RR** is ***doubled***, and V_T is ***reduced to half***:
  1. **RMV** ⇨ ***no change***, however
  2. **AV** ⇨ will be ***halved***.

Forced Expiratory Volume

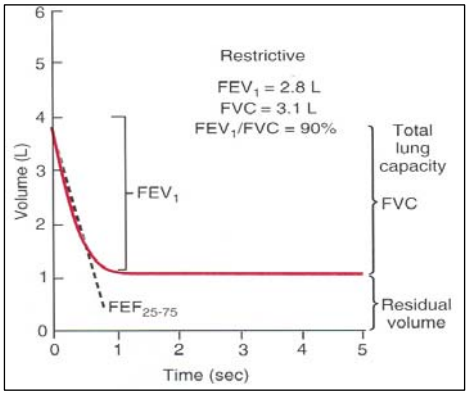
- **Forced expiratory volume** (FEV) is a test in which the percentage of the vital capacity that can be exhaled in the first second (FEV_1) is measured, and is considered one of the most reliable spirometer measurements.
  - FEV_1 can be expressed as a percentage of FVC (i.e., $FEV_1/FVC \times 100$), which corrects for difference in lung size.
  - Normally, FEV_1/FVC% is **80%** ⇨ meaning 80% of an individual's FVC can be exhaled in the first second of forced vital capacity.
  - **Note**: Any percentage significantly below 80% suggests the presence of **obstructive pulmonary disease**.



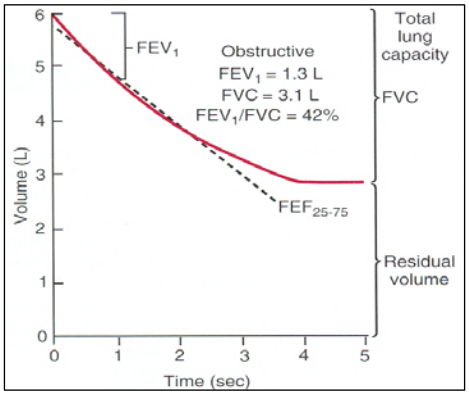
- **FVC, FEV_1/FVC** and FEF_{25-75} are used to detect the restrictive and obstructive disorders.
- In a normal lung:
  - **FEV_1 = 4 L** (in the first second)**.**
  - **FVC = 5 L** (total volume expired).
  - **FEV/FVC = 80%**

Restrictive and Obstructive Disorders

- In **restrictive disorders** (e.g., *pulmonary fibrosis*, *pleural effusion*, *pneumothorax*, *haemothorax*, and *lung tumors*), the vital capacity is reduced below normal. The problem is in the inspiration; however the expiration is not affected.
  - **FVC** can fall **below 3 L** in *restrictive pulmonary disease*.

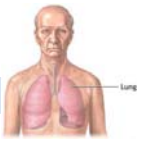


- In **obstructive disorders** (e.g., *acute asthma*, *emphysema*, an*chronic bronchitis*), the vital capacity is usually normal because lung tissue is not damaged, but expiration is more difficult and takes a longer time because bronchoconstriction increases the resistance to air flow.
- RV increases as it is not emptied by the time the next breath starts.
- $FEF_{25—75}$ is reduced.
  - **FEV_1** significantly **below 80%** is used to diagnose *obstructive pulmonary disease*.

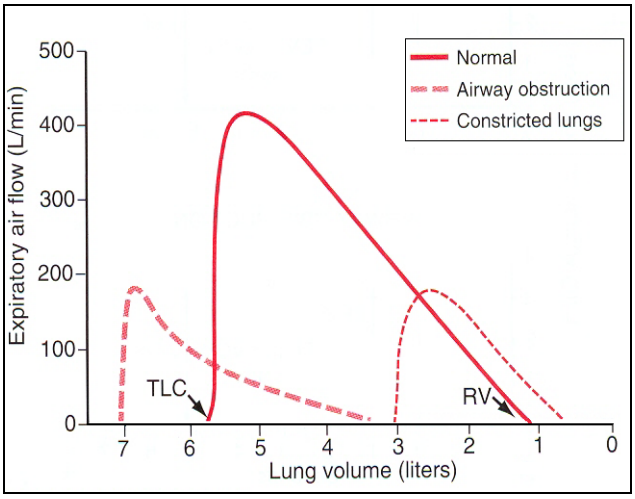


Maximum Expiratory Flow (Forced Expiratory Flow)

- When a person expires with great force, the air coming out of the lung (expiratory airflow) reaches a maximum flow (or speed) beyond which the flow cannot be increased with greatly increased additional force. This is the **maximum expiratory flow**.
  - This measurement represents the expiratory flow rate over the middle half of the forced vital capacity (between 25 and 75%).
  - The normal ***forced expiratory flow*** (FEF) equals or is higher than **400 L/min**.



- In diseases with **constricted lungs** (e.g., *tuberculosis* and *scoliosis*), the effect **reduces** total lung capacity (**TLC**) and reduces residual volume (**RV**).
  Furthermore, because the lung cannot expand to a normal maximum volume, the *maximum expiratory flow* can fall below **200 L/min**.
- In diseases with **airway obstruction** (e.g., *asthma* and *emphysema*), air tends to enter the lungs easily but then become trapped in the lungs. Over a long period, this effect **increases** both the **TLC** and **RV**. Also because of the obstruction of the airways and because they collapse more easily than normal airways, the *maximum expiratory flow* can fall below **200 L/min**.

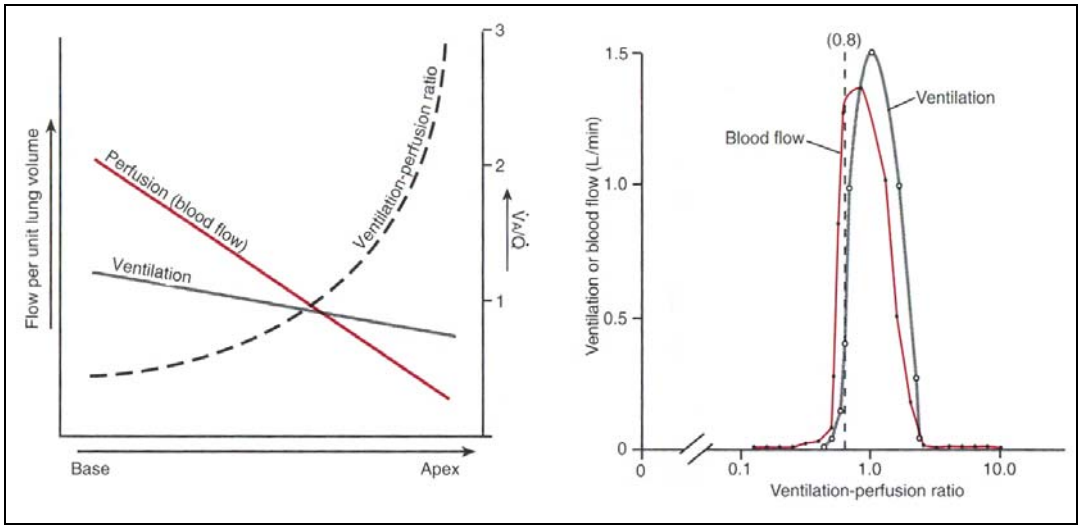


Ventilation/Perfusion (V_A/Q) Ratios

- It is the ratio of alveolar ventilation (V_A) to blood flow or perfusion (Q) in lung regions.
- Importance of matching alveolar ventilation with blood flow is that it is *the crucial factor in gas exchange*.
- There are three important points to remember:
  - Ventilation and blood flow are both gravity-dependent; airflow and blood flow increase down the lung.
  - Blood flow shows about a 5-fold difference between the top and bottom of the lung, while ventilation shows about a 2-fold difference. This causes gravity-dependent regional variations in the V_A/Q ratio that range from **0.6 at the base** to **3.0 or higher at the apex**.
  - Blood flow is proportionately greater than ventilation at the base, and ventilation is proportionately greater than blood flow at the apex.
- In healthy individuals with alveolar ventilation (V_A) of 4 L/min and cardiac output (pulmonary blood or perfusion) of 5 L/min, the ideal alveolar ***ventilation-perfusion ratio*** (V_A/Q) should be **0.8**.

	Ventilation (V_A) (L/min)	**Blood Flow (Q)** (L/min)	**Ratio (V_A/Q)**
Apex	0.25	0.07	**3.6**
Base	0.8	1.3	**0.6**

***Note**: There is slight overventilation (wasted ventilation) at the apex of the lung where V_A/Q is high, and the opposite occurs at the base where there is slight over-perfusion (wasted perfusion) and V_A/Q is low.*



Gas Exchange

- Gas exchange in the lungs occurs across an estimated **300 million alveoli**, each with a *diameter* between **0.25 to 0.5 mm** (smaller than a red blood cell, which must squeeze through the capillary). Their enormous number provides a large *surface area* of about **70 m^2**, or about **760 square feet** for diffusion of gases.
- The amount of *blood volume* spread over the entire surface of lung capillaries is about **60-140 ml** at any given moment.
- *Respiratory membrane*, through which gas exchange occurs, is composed of an alveolar membrane and a capillary membrane. Both capillary and alveolar membranes are only one cell-layer thick, so that the "air-blood barrier" is only two cell membranes thick, or about **2 µm**.
- The *diffusion distance* between blood and air can be as little as **0.3 µm**, which is about $^{1}/_{100}^{th}$ the width of a human hair.

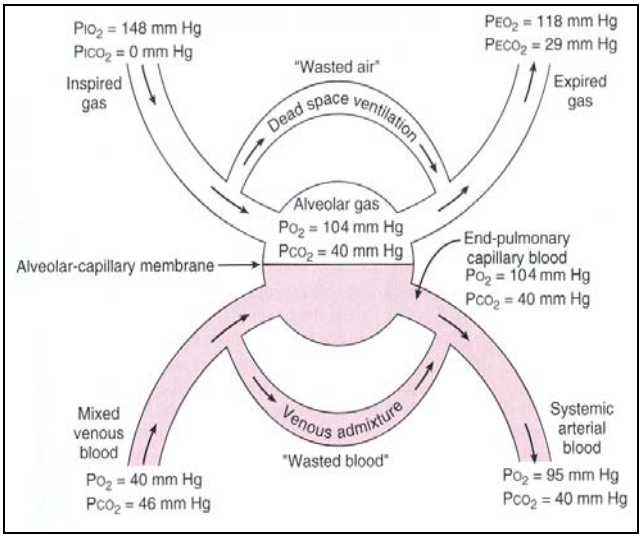
Factors Affecting Rate of Gas Diffusion Through Respiratory Membrane:

1) **Thickness** of the respiratory membrane:
   - Because the rate of diffusion through the membrane is inversely proportional to the thickness of the membrane, any factor that increases the thickness will decrease the normal respiratory exchange significantly (e.g., *edema*, and *pulmonary fibrosis*).

2) **Surface area** of the respiratory membrane:
   - Any decrease in the total surface area will impede the change of gases through the membrane to a significant degree, even under resting conditions (e.g., *emphysema*, or *surgical removal of the lung or part of the lung*).

3) **Partial pressure difference** across the respiratory membrane:
   - It is the difference between the partial pressure of the gas in the alveoli and the pressure of the gas in the pulmonary capillary, and is a measure of the *net tendency* for the gas molecules to move through the membrane.
   - The partial pressure of oxygen (P_{O2}) in:
     - Alveoli: **104 mmHg**,
     - In pulmonary capillaries: **40 mmHg** at arterial end and reaches **104 mmHg** at venous end,

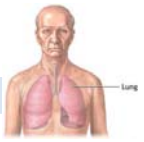
   ⇨ Difference in P_{O2} leads to diffusion of oxygen from alveoli to the capillary blood until it is becomes saturated at the venous end.



4) **Diffusion coefficient** of the gas:
   - Depends on two factors:

   ❶ ***Solubility*** *of the gas in the membrane*: The higher the solubility the greater the diffusion (CO_2 diffuses about 20 times as rapidly as O_2).

   ❷ ***Square root*** *of the gas's* ***molecular weight***: Inverse relationship; the smaller the square root, the greater the rate of diffusion.



The "Work" Breathing

- The **basal metabolism** is the minimum energy needed for maintenance of respiration, circulation, peristalsis, muscle tone, body temperature, glandular activity, and other vegetative (e.g., asleep) functions of the body.
- **Basal metabolic rate** (BMR), measured by the rate of oxygen consumption, averages about **2000 kcal/day**.
  - Work of breathing ***increases*** in a resting stage with:
    ① **Obstructive lung diseases** (e.g., asthma and emphysema).
    ② **Decrease of surfactant**: Sufficient surfactant decreases the work of breathing.
    ③ **Restrictive lung diseases** (e.g., haemothorax).

Transport of Oxygen

- After gas transfusion in the lungs, normally, 98% of the oxygen is transported in chemical combination with **hemoglobin** in the red blood cells, while the remaining 2% is transported in the dissolved state in **plasma** to supply Retina and Cartilage.
  - Dissolved O_2 = 0.3 ml/100 ml blood when P_{AO2} equals 100 mm Hg).
  - Fetal Hemoglobin (HbF) has more affinity to O_2 than adult hemoglobin (HbA).

◈ *Structure of Hemoglobin*:

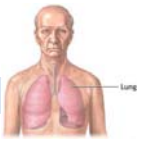
- Each hemoglobin molecule consists of four oxygen-binding heme sites and four globular protein chains.
- In the center of each heme group is one atom of reduced iron (Fe^{2+}, or ferrous iron), which can combine loosely and reversibly with one molecule of oxygen to form **oxyhemoglobin** (HbO_2).
- **One molecule of hemoglobin** can thus combine with **four molecules of oxygen** – and since there are about 280 million hemoglobin molecules per red blood cell, each red blood cell can carry over a billion molecules of oxygen.

$$\mathbf{O_2 + Hemoglobin \rightleftharpoons Oxyhemoglobin}$$

- Hemoglobin concentration in blood equals **15 gm/100 ml of blood**.
- Each gram of hemoglobin can combine with **1.34 ml of O_2** ⇨ On average; the hemoglobin in 100 ml of blood can combine with a total of **20 ml of O_2**, this is the maximum amount of oxygen that can be carried by hemoglobin and is called the **oxygen carrying capacity** (20 ml O_2/100 ml blood).
- ✵ **Note**: The 98% of oxygen transported in combination with hemoglobin is the **full saturation** of hemoglobin by oxygen.

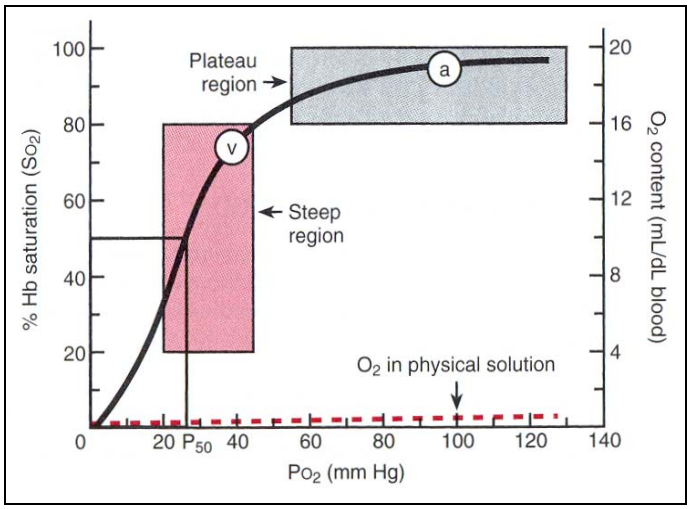
◈ *The Oxyhemoglobin Dissociation Curve*:

- It is a **sigmoid** (S-shaped) curve that shows the relationship between P_{O2} (partial pressure of oxygen), hemoglobin saturation, and oxygen content.
- ✵ **Note**: The shape of the curve results because the hemoglobin affinity for oxygen increases progressively as blood P_{O2} increases.



Arterial Blood:-

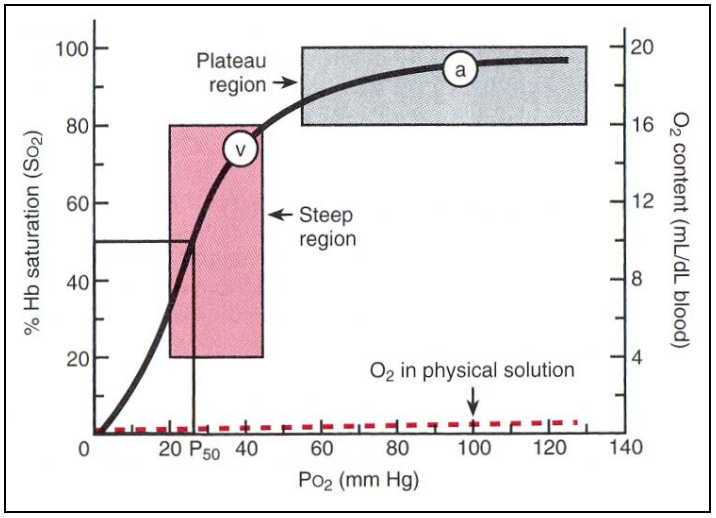
- At a partial pressure (P_{O2}) of 100 mmHg ⇨ there is full saturation of hemoglobin at **98%.**
- Full saturation of hemoglobin occurs in the lungs.
- At full saturation, the concentration of O_2 in arterial blood is about 20 ml/100 ml blood.
- **Plateau region**: called the **loading phase** in which oxygen is loaded onto hemoglobin to form oxyhemoglobin in the pulmonary capillaries.



- **1st Observation**: P_{AO2} can increase from 100 mmHg to 120 mmHg with minimum change in hemoglobin saturation, increasing only by 1% from 98% to 99% ⇨ therefore, hyperventilation (e.g., during exercise) does not change the saturation of hemoglobin with oxygen significantly.
- **2nd Observation**: P_{AO2} can decreases from 100 mmHg to 70 mmHg with minimum change is hemoglobin saturation, decreasing only by 4% from 98% to 94% ⇨ this is important, because at high altitudes or in certain lung diseases the P_{O2} may decrease from 100 mmHg to 70 mmHg with a minimum change in hemoglobin saturation.

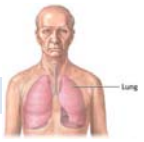
Venous Blood:-

- Venous blood P_{O2} = 40 mmHg ⇨ saturation of venous blood is about **75%.**
- At full saturation, the concentration of oxygen in venous blood is about 15 ml/100 ml blood.
- P_{O2} = 40 mmHg causes the release of oxygen from hemoglobin ⇨ this amount that is released from hemoglobin (98% to 75%) is required for the release of oxygen from hemoglobin and is *required by the body to provide oxygen to the tissues* at which P_{O2} is about 40 mmHg (in mixed venous blood = pulmonary artery).
- If P_{O2} drops below 40 mmHg ⇨ causes acute desaturation of hemoglobin of oxygen and this is not required by the body and is incompatible with life ⇨ causes **tissue anoxia**.



- The **steep region** in the graph is due to the increase of affinity of hemoglobin for oxygen with each oxygen atom that becomes attached to it.

✺ **Note**: The S-shaped oxyhemoglobin equilibrium curve enables oxygen to saturate hemoglobin under high partial pressures in the lungs and to give up large amounts of oxygen with small changes in P_{O2} at tissue level.



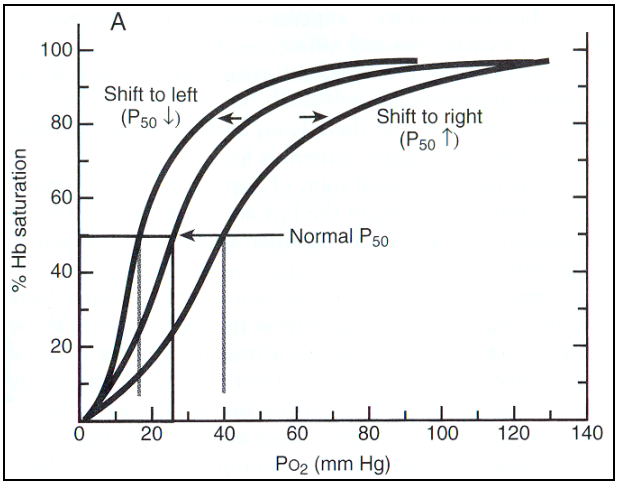
P_{50}:-

- P_{50} is the partial pressure of oxygen at which 50% of hemoglobin is saturated.
- P_{50} is a good measure of hemoglobin's affinity to oxygen, and provides a functional way to assess the binding affinity of hemoglobin for oxygen.
- The normal P_{50} for arterial blood is **26 – 28 mmHg**.
- ↑ P_{50} ⇨ ↓ Hb affinity for O_2 and results in a rightward shift in the oxyhemoglobin equilibrium curve, whereas any ↓ P_{50} ⇨ ↑ Hb affinity for O_2 and shifts the curve to the left.

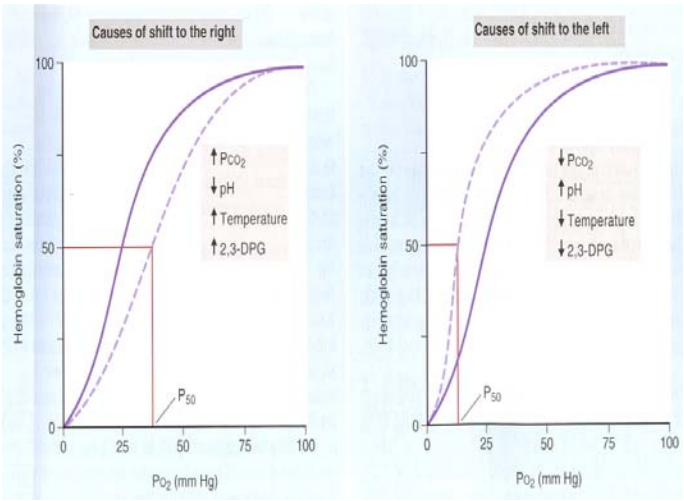
✺ **Note**: The coronary artery contains about 20 ml O_2/100 ml blood but contains only **5 ml O_2/100 ml blood** left in the coronary sinus; hence, the heart uses most of its oxygen and has a small O_2 reserve.

◈ *Physiological Factors that Affect Oxyhemoglobin Curve:-*

- If the curve shifts to the right ⇨ indicates less affinity of hemoglobin for oxygen (P_{50} increases) ⇨ more oxygen available to the tissues.
- If the curve shifts to the left ⇨ indicates higher affinity of hemoglobin for oxygen (P_{50} decreases) ⇨ less oxygen available to the tissues.
- A shift in the P_{50} in either direction has the greatest affect on the steep phase and only a small affect on the loading of oxygen in the normal lung, because loading occurs at the plateau.



- Factors that shift the curve to the right (↑P_{50}):
  ① ↑ Body temperature (e.g., exercise).
  ② ↑ H^+ ions (↓pH) – acidosis (because tissues need more O_2 to convert lactate to pyruvate) (e.g., exercise).
  ③ ↑ P_{CO2} (e.g., exercise).
  ④ ↑ 2,3 Diphosphoglycerate (2,3-DPG).
- Factors that shift the curve to the left (↓P_{50}):
  ① ↓ Body temperature (e.g., cold weather).
  ② ↓ H^+ ions (↑pH) – alkalosis.
  ③ ↓ P_{CO2}.
  ④ ↓ 2,3-DPG.



- In the winter, people with white skin who stand in the cold have red cheeks because the temperature of their faces are less than the rest of their body (the oxyhemoglobin curve shifts to the left side and hemoglobin affinity for oxygen increases), more hemoglobin binds to O_2 which causes the red cheeks.

◈ *Resting O_2 Consumption*:

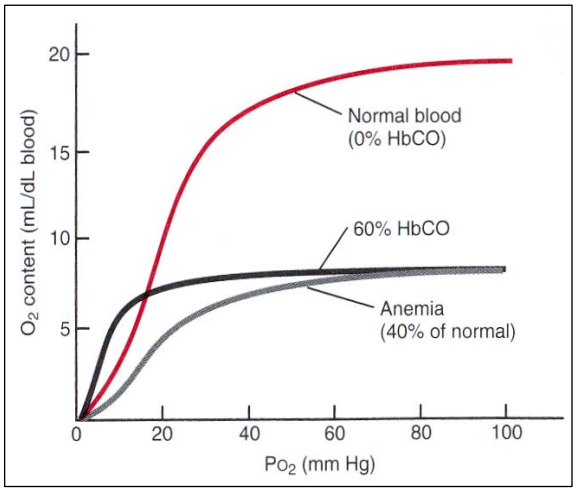
- Arterial blood contains 20 ml O_2/100ml blood, and venous blood contains 15 ml O_2/100 ml blood ⇨ tissues receive 5 ml of O_2 out of every 100 ml of blood.
- Each 100 ml of blood gives 5 ml of oxygen at rest ⇨ In 1 minute; our bodies consume **250 ml** of oxygen.

✺ **Note**: The coronary artery, however, has 20 ml O_2/100 ml blood while the coronary sinus only has 5 ml O_2/100 ml blood left ⇨ The heart consumes **750 ml** of oxygen per minute.

◈ *Affect of Blood Hematocrit and CO on the Oxyhemoglobin Equilibrium*:

Anemia: A decreased number of circulating red blood cells.

- Saturation is normal, P_{O2} is the same but the amount of O_2 in the blood is less (almost half of normal).
- Oxygen content, rather than P_{O2} and Hb saturation, is what keeps us alive. Therefore, the amount of O_2 in the blood is more important than P_{O2} and Hb saturation.
- Curve shifts to the right side.



Carbon monoxide poisoning:

- CO competes with O_2 for the same binding sites on hemoglobin (0.1% CO can replace half the O_2 & combine with about 50% of hemoglobin if found in the air).
- Dangers of CO:
  ① As a colorless, odorless, and nonirritating gas, it is virtually undetectable.
  ② Has a binding affinity 210 times that of oxygen.

❑ The best treatment for CO poising is breathing 100% oxygen or a mixture of 95% O_2 / 5% CO_2. Since O_2 and CO compete for the same biding site on the hemoglobin molecule, breathing high oxygen concentration will drive off the CO and favor the formation of oxyhemoglobin.

TRANSPORT OF CARBON DIOXIDE

Normally **4 ml of CO_2** is transported from the tissues to the lungs in each 100 ml blood ⇨ **200 ml of CO_2** are transported to the lungs per minute in normal conditions.

Gaseous CO_2 (generally not bicarbonate) diffuses out of the cell:

Carbon dioxide (CO_2) is carried in the blood in three forms:

1) **Dissolved in plasma (7%)**:

- The high P_{CO2} in the tissues (45 mm Hg) drives CO_2 into the blood.
- CO_2 is 20 times more soluble than oxygen in water.
- Arterial blood (entering the tissues) P_{CO2} = 40 mmHg ⇨ 2.4 ml CO_2 in 100 ml blood.
- Venous blood (leaving the tissues) P_{CO2} = 45 mm Hg ⇨ 2.7 ml CO_2 in 100 ml blood.

→ Therefore, only about **0.3 ml CO_2/100 ml blood** is transported in the form of dissolved carbon dioxide.

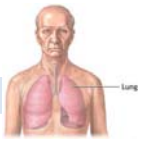
2) **Carbaminohemoglobin** (23%):

- CO_2 combines reversibly with an amino acid in hemoglobin (and to a much lesser extent other plasma proteins to form **carbamino proteins**).

3) **Bicarbonate ions (70%)**:

- CO_2 combines with water in RBCs to form carbonic acid (H_2CO_3); this reaction is accelerated 5,000 times in RBCs by the enzyme **carbonic anhydrase**.

✺ **Note**: Only a small amount of carbon dioxide stays as dissolved CO_2 in the plasma. The bulk of the carbon dioxide diffuses into the red cell, where it forms either **carbonic acid** (H_2CO_3) or **carbaminohemoglobin**.



I. **Carbaminohemoglobin**:

- Carbaminohemoglobin is formed in RBCs from the reaction of CO_2 with free amine groups (NH_2) on the hemoglobin molecule (deoxygenated hemoglobin can bind much more CO_2 in this way than oxygenated hemoglobin).

$$\mathbf{Hb + CO_2 \leftrightarrow Hb\text{-}CO_2\ (}\boldsymbol{carbaminoheamoglobin}\mathbf{)}$$

✵ **Note**: The bulk of the CO_2 is actually transported in the plasma in the form of bicarbonate.

II. **Bicarbonate**:

- In the RBC, the **carbonic acid** is formed in the following manner: $\mathbf{CO_2 + H_2O \overset{\text{carbonic anhydrase}}{\rightleftharpoons} H_2CO_3}$
- Carbonic acid dissociates in RBCs to bicarbonate (HCO_3^a) and H^+: $\mathbf{H_2CO_3 \rightleftharpoons H^+ + HCO_3^-}$

(1) **HCO_3^a**:

- HCO_3^a leaves the RBCs giving it a net positive charge, and this attracts **chloride ions** (Cl^a) which diffuses into the RBC from the plasma maintaining the electrical neutrality.
- **THE CHLORIDE SHIFT**: The chloride movement from the plasma into the RBCs in exchange for HCO_3^a is known as the **chloride shift** and is facilitated by the *bicarbonate-chloride carrier protein* **(anion exchanger)** in the RBC membrane.

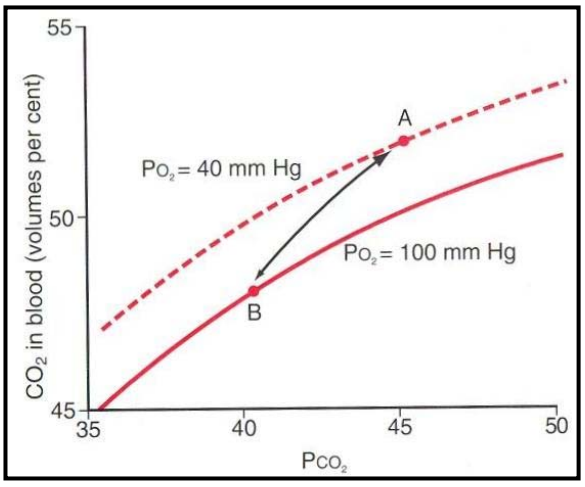
(2) **H^+** :

- H^+ cannot move out because of the low permeability of the RBC membrane to H^+.
- Most of the H^+ is buffered by **hemoglobin** (Hb is a powerful **acid-base buffer**).
- As H^+ binds to hemoglobin: $\mathbf{H^+ + HbO_2^a \rightleftharpoons HHb + O_2}$
  - ⇨ (a) It <u>decreases</u> the **oxygen binding** & (b) shifts the **oxyhemoglobin equilibrium curve** to the <u>right</u>,
  - ⇨ (c) this promotes <u>unloading</u> of **oxygen** from hemoglobin in tissues and (d) <u>favors</u> the carrying of **CO_2**.
  - → Thus, CO_2 increases oxygen unloading, and oxygen unloading increases CO_2 transport.

✵ **Note**: In pulmonary capillaries, the oxygenation of hemoglobin favors the unloading of carbon dioxide.

CARBON DIOXIDE EQUILIBRIUM CURVE:

- The carbon dioxide equilibrium curve is nearly a straight-lined function of P_{CO2} in the normal arterial CO_2 range.
- **THE HALDANE EFFECT**: Binding of oxygen with hemoglobin tends to displace carbon dioxide from the blood (↑P_{O2} will shift the curve downward and to the right) ⇨ its advantage is that it allows the blood to load more CO_2 in the tissues and unload more CO_2 in the lungs.
- In the lungs, ↑ P_{O2} → ↓ affinity to CO_2
- In tissues, ↓ P_{O2} → ↑ affinity to CO_2



- Combination of oxygen with hemoglobin in the lungs ⇨ **↑ Acidity of hemoglobin** (the hemoglobin becomes a stronger acid) ⇨ displaces CO_2 from the blood and into the alveoli in two ways:
  (1) ↓ Hemoglobin combining with CO_2 to form carbaminohemoglobin.
  (2) ↑ Hemoglobin release of H^+ ⇨ H^+ binds with bicarbonate ions to form carbonic acid ⇨ dissociates into H_2O and CO_2 ⇨ CO_2 is released from the blood into the alveoli.

✵ **Note**: Oxygenated hemoglobin has <u>less</u> affinity to combine with CO_2, while deoxygenated hemoglobin has <u>more</u> affinity to combine with CO_2.

Reactions of Carbon Dioxide in the Blood

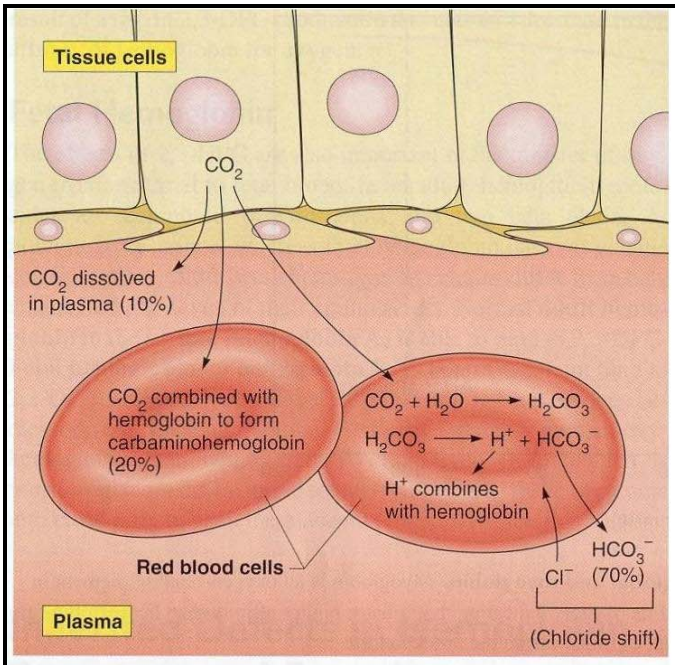


Figure 16.38 Carbon dioxide transport and the chloride shift. Carbon dioxide is transported in three forms: as dissolved CO_2 gas, attached to hemoglobin as carbaminohemoglobin, and as carbonic acid and bicarbonate. Percentages indicate the proportion of CO_2 in each of the forms. Notice that when bicarbonate (HCO_3^-) diffuses out of the red blood cells, Cl^- diffuses in to retain electrical neutrality. This exchange is the chloride shift.

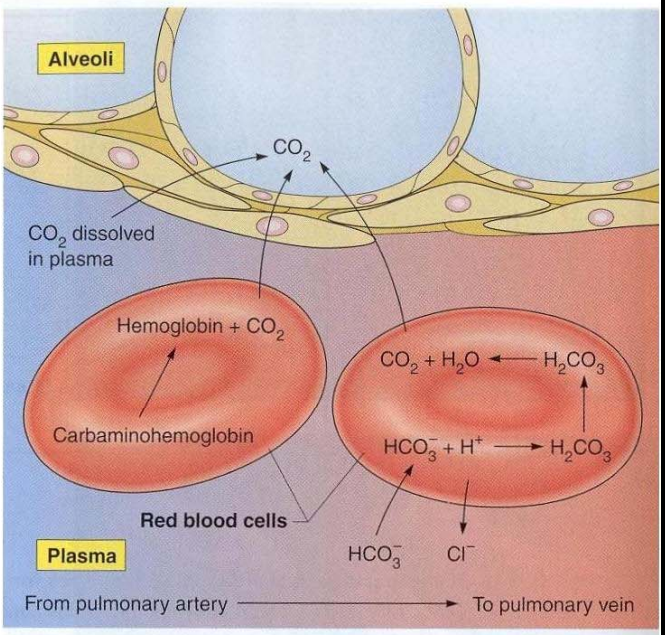
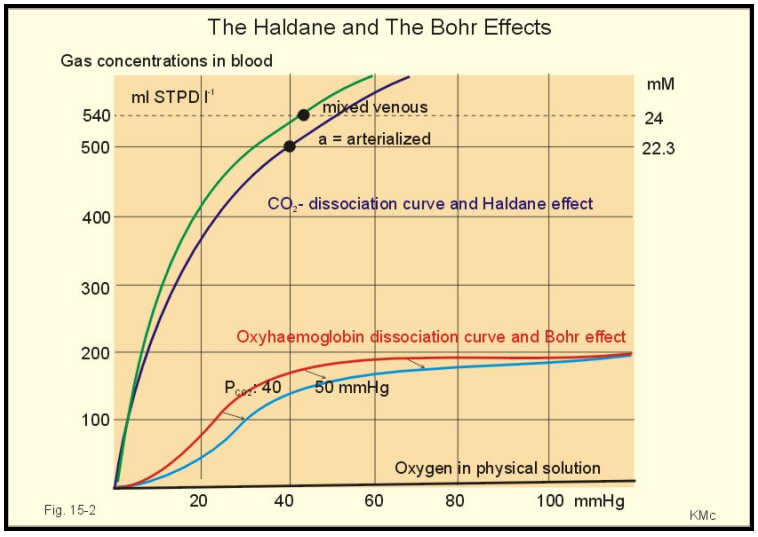
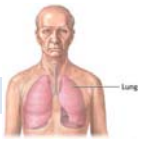


Figure 16.39 The reverse chloride shift in the lungs. Carbon dioxide is released from the blood as it travels through the pulmonary capillaries. A "reverse chloride shift" occurs during this time, and carbonic acid is transformed into CO_2 and H_2O. The CO_2 is eliminated in the exhaled air.

Differences between Carbon Dioxide & Oxygen Equilibrium Curves:

- First, one liter of blood can hold much more carbon dioxide than oxygen.
- Second, the CO_2 equilibrium curve is steeper and more liner (no plateau phase), and because the shape of the CO_2 equilibrium curve, large amounts of CO_2 can be loaded and unloaded from the blood with a small change in P_{CO2} ⇨ this is important in both gas exchange and in the regulation of acid-base balance.





Blood Acidity during Carbon Dioxide Transport:

- Arterial blood has a pH of about 7.41, and as the blood acquires CO_2 in the tissue capillaries, the pH falls to a venous value of 7.37 ⇨ a pH change of 0.04 unit takes place, and the reverse occurs when CO_2 is released from the blood in the lungs, raising the pH back to the arterial value.

✺ **Note**: During high metabolic activity (e.g., heavy exercise) or when the blood flow to the tissues is sluggish, the decrease in the tissue blood and the tissues themselves can be as much as **0.50** (12 times normal) causing significant tissue acidosis.

☞ Binding of CO_2 leads to ↓ pH of blood (venous blood)

☞ Release of CO_2 leads to ↑ pH of blood (arterial blood)

Respiratory Exchange Ratio:

- Normal transport of oxygen from the lungs to the tissues by each 100 ml of blood is about 5 ml, whereas normal transport of carbon dioxide from the tissues to the lungs is about 4 ml.
- Thus, under normal resting conditions, only about 82% as much carbon dioxide is expired from the lungs as there is oxygen uptake by the lungs.
- The ratio of carbon dioxide output to oxygen uptake is called the *respiratory exchange ratio* (R):

$$\mathbf{R = \frac{CO_2\ output}{O_2\ uptake}}$$

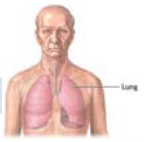
- Normal diet, consuming average amounts of carbohydrates, fats, and proteins, the average value for R is equal to 4/5 = **0.825**.
- The value for R changes under different metabolic conditions:
  1. **Carbohydrate diet** (↑R): One molecule of CO_2 is formed for each molecule of O_2 ⇨ **R = 1.00**.
  2. **Fat diet** (↓R): More O_2 combines with H^+ from fats to form water instead of CO_2 ⇨ **R = 0.7**.

Regulation of Respiration

Intro:-

- Breathing is an **autonomic process** (involuntary) that occurs without any conscious effort while we are awake, asleep, or under anesthesia.
- The unconscious rhythmic control of breathing is influenced by sensory feedback from receptors sensitive to the P_{CO2}, pH, and P_{O2} of arterial blood.
- Breathing is similar to the heartbeat in terms of autonomic rhythm, but it also differs in 2 ways:

1. There is no single pacemaker that sets basic rhythm of breathing, while the heart only has the S.A. node.
   ⇨ Control of muscle excitation in breathing is the result of **multiple neuronal interactions** involving *all levels of the nervous system*.
2. No single muscle is devoted solely to breathing, while the heart only has the cardiac muscle.
   ⇨ Breathing depends on the cyclic excitation of **many muscles** that can influence the volume of the thorax.



Mechanisms of Control:-

A. **Neural control mechanism**:

- Respiratory centers are composed of several groups of neurons located bilaterally (on both sides) in the **medulla oblongata & pons** (brain stem):

(1) **Dorsal Respiratory Group** (*medulla*):

- Location: in the dorsal portion of the medulla. It contains the termination of the vagal & glossopharyngeal nerves, which transmit sensory signals from (a) the peripheral chemoreceptors, (b) the baroreceptors, and (c) several types of receptors in the lung.
- Function: maintains the basic rhythm of respiration ⇨ It is responsible for **initiation of inspiration** (whether quiet or deep) by stimulating contraction of the diaphragm.
- Mechanism: Transmits nervous signals to the primary inspiratory muscles (mainly the diaphragm) begins weakly and increases steadily in a **ramp manner** for about 2 seconds (causing steady inspiration) and then ceases abruptly for the next 3 seconds ⇨ turns off excitation of the diaphragm and allows elastic recoil of the lungs and chest (causing expiration).

❋ **Note**: The obvious advantage of the ramp is that it causes a steady increase in the volume of the lungs during inspiration, rather than inspiratory gasps.

(2) **Pneumotaxic center** (*pons*):

- Location: dorsally in the upper pons.
  - Functions to (a) limit inspiration, and (b) regulate the rate of respiration ⇨ by inhibiting the **dorsal respiratory group** when the tidal volume reaches **500 ml**.
- Mechanism: it controls the "**switch-off**" point of the inspiratory ramp, thus controlling the duration of the filling phase of the lung cycle.

❋ **Note**: Damage to the *pneumotaxic center* will cause an increase in tidal volume ($\uparrow V_T$) by increasing the duration of inspiration ⇨ causes **gasping**, because of lack of inhibition to the dorsal respiratory group, and it will also decrease the respiratory rate ($\downarrow$RR).

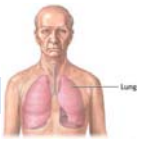
(3) **Apneustic center** (*pons*):

- Located: dorsally in the lower portion of the pons.
- Function: **Inhibits the "switch-off"** of inspiratory ramp signals, and therefore increases duration of inspiration ⇨ lung becomes almost completely filled with air, and short expiratory gasps occur.

(4) **Ventral Respiratory Group** (*medulla*):

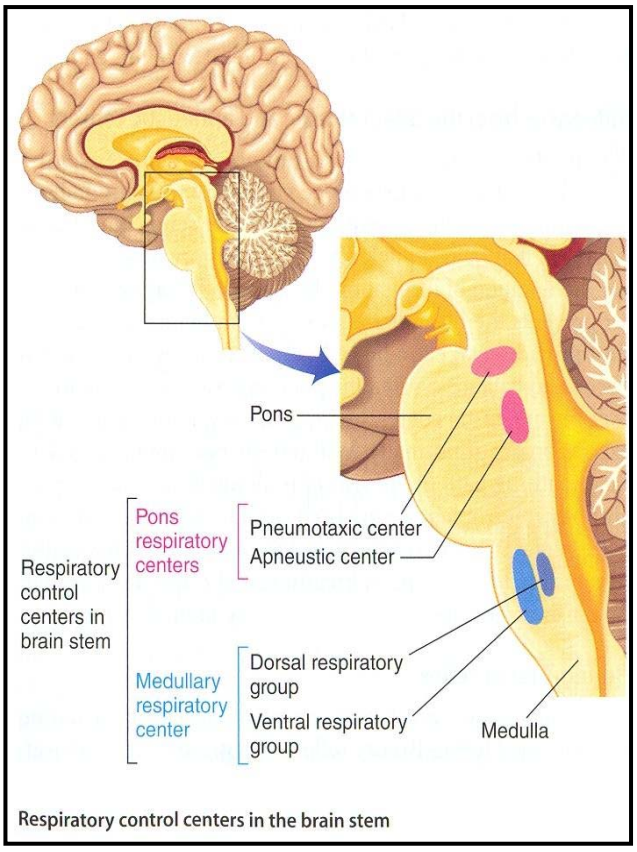
- Location: in the ventrolateral portion of the medulla. It contains both inspiratory (when stimulated cause inspiration) and expiratory neurons (when stimulated cause expiration).
- Function: Normally **inactive** during quiet respiration ⇨ active during **deep** (forced) **expiration** and **inspiration**.
- Mechanism: When the respiratory drive for increased pulmonary ventilation becomes greater than normal (e.g., during exercise), respiratory signals spill over into the ventral respiratory neurons from the dorsal respiratory area ⇨ the ventral respiratory group then contributes to the respiratory drive.

(5) **Cerebral Cortex**: It regulates voluntary respiration (e.g., singing, and speaking).



❑ *Summary of Mechanism of Control:*

- ◈ *The **dorsal respiratory group** plays the most fundamental role in control of respiration. It is responsible for the basic rhythm of respiration.*
- ◈ *A decrease in the duration of inspiration also causes a decrease in the duration of expiration and this will increases the rate of respiration.*
- ◈ *A strong **pneumotaxic** signal decreases inspiration (0.5 seconds) and increase the rate of breathing to 30 or 40 breaths per minute. While a weak pneumotaxic signal increases inspiration (5 seconds) and reduce the rate of breathing to only 3 to 5 breaths per minute.*
- ◈ *The **ventral respiratory group** does not participate in the basic rhythm of respiration.*
- ◈ *The **apneustic center** appears to promote inspiration by sending signals to the dorsal respiratory group of neurons to prevent or retard the "switch-off" of the inspiratory ramp signal.*



Respiratory control centers in the brain stem

B. **Reflexes**:

1) **Slowly adapting receptors** (**Hering-Breuer reflex**):

- ➢ When the tidal volume reaches 1.5 L in the airways causing them to stretch, *pulmonary stretch receptors* in the conducting airways send a feedback signal through the vagus nerve that inhibits the dorsal respiratory group in the medulla ⇨ stopping inspiration.
- ➢ It is a **protective mechanism** that prevents excess inflation of the lung (therefore, it is also called **lung inflation reflex**) and is not important during normal control of ventilation.

✺ **Note**: The Hering-Breuer reflex is much like the pneumotaxic center in that it "switches-off" the inspiration ramp signal in the dorsal respiratory group. The difference is that Hering-Breuer reflex works only during deep inspiration while the pneumotaxic center works during normal inspiration.

2) **Rapidly adapting receptors**:

(a) **Irritant receptors**:

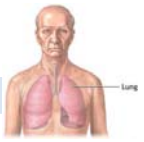
- ➢ Sensory fibers found in the larger conducting airways, respond to irritations of the airways by touch or by noxious (chemical) substances (e.g., smoke and dust).

(b) **Juxtapulmonary capillary receptors** (**J receptors**):

- ➢ The nerve endings are located near adjacent to the alveoli and are in the pulmonary capillaries, and are stimulated by lung injury, edema, congestion, and pulmonary embolism.
- ➢ They cause rapid shallow breathing, bronchoconstriction, increased mucus secretion, and apnea

3) **Proprioceptors**: receptors in joints, tendons, & muscles play a role in breathing (e.g., exercise).

✺ **Note**: An increase in body temperature can stimulate the respiratory center to increase the respiratory rate.



C. **Chemoreceptors**: They are receptors sensitive to the chemical composition of the blood.

- Two groups of chemoreceptors respond to changes in blood P_{CO2}, pH, and P_{O2}:

1) **Peripheral chemoreceptors**: control breathing indirectly via sensory nerve fibers to the medulla.

a) **Aortic bodies**: located around the aortic notch, they send sensory information to the medulla in the vagus nerve (X).

b) **Carotid bodies**: located in each common carotid artery where they branch into the internal & external carotid artery, they stimulate sensory fibers in the glossopharyngeal nerve (IX).

- The peripheral chemoreceptors are stimulated by an increase in P_{ACO2}, increase H^+ concentration (fall in pH, acidosis) in arterial blood, and a fall in P_{AO2} (hypoxia)
  - ⇨ ↑ P_{ACO2}, ↑ H^+, ↓ pH, ↓ P_{AO2}.

✺ **Note**: The peripheral chemoreceptors are not stimulated directly by blood CO_2. They are stimulated by rise in H^+ (↓pH), which occurs when blood CO_2, thus carbonic acid, is raised.

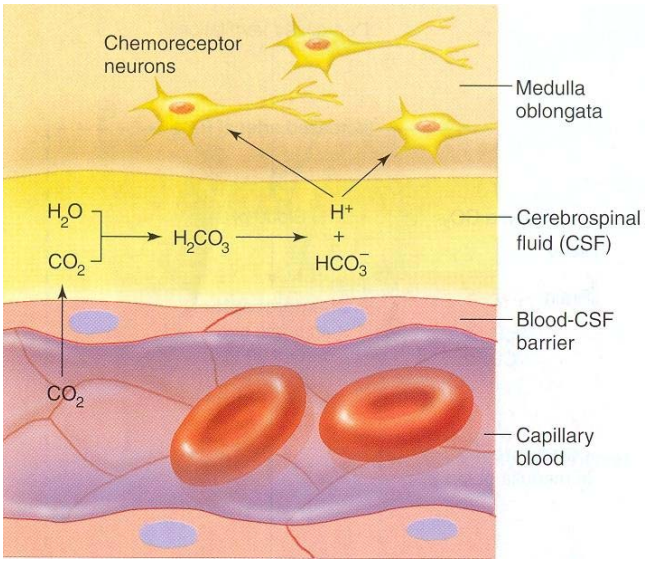
- *The aortic and carotid bodies should not be confused with the aortic and carotid **sinuses** that contain receptors that monitor the blood pressure.*

2) **Central chemoreceptors** (*in the medulla oblongata*):

- The central chemoreceptor is most sensitive to changes in arterial P_{CO2}:

An increase in arterial P_{CO2} causes a rise in the H^+ concentration of the blood as a result of increased carbonic acid concentrations:

- The H^+ in the blood cannot cross the blood-brain barrier, and therefore cannot influence the medullary chemoreceptors.
- CO_2 in the arterial blood *can* cross the blood-brain barrier and, through the formation of carbonic acid, can lower pH of cerebrospinal fluid ⇨ this stimulates the chemoreceptors in the medulla when there is a rise in a arterial P_{CO2}.

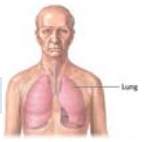


✺ **Note**:

- Chemoreceptors cannot be consciously suppressed, so you cannot kill yourself by holding your breath
- Changes in blood P_{CO2} are 10 times more affective on ventilation and in controlling respiration than changes in blood pH.
- Before beginning an exercise, there is an increase in the respiratory rate, even if no stimulation for receptor or movement of joints start.

D. **Voluntary Control of Respiration**:

- **During**: breathe holding, talking, swimming, singing, etc.
- It is a function of the **cerebral cortex**.
- Anticipation of severe exercise → ↑ respiratory rate & ↑ C.O. by sympathetic stimulation.



Effects of Blood P_{O_2} on Ventilation:-

- Arterial P_{O2} is monitored by the **peripheral chemoreceptors**.
- The peripheral chemoreceptors are not sensitive to modest changes in arterial P_{O2}. Under normal conditions, P_{AO2} affects breathing only indirectly by influencing the chemoreceptor's sensitivity to P_{CO2}.
- The arterial P_{O2} must fall below **60 mm Hg** (>40% reduction) before they directly stimulate the peripheral chemoreceptors (when it reaches this point, the ventilation rate doubles).
- Because the peripheral chemoreceptors respond to blood $P_{O2,}$ and *not* the total O_2 content, O_2 content in the arterial blood can fall to dangerously low or even fatal levels (e.g., anemia, CO poisoning) without simulating the peripheral chemoreceptors because P_{AO2} remains normal, so respiration is not stimulated.

❑ *There is no need to increase ventilation until P_{AO2} falls below 60 mm Hg, because of the safety margin in % Hb saturation afforded by the plateau portion of the oxyhemoglobin curve. Hemoglobin is still 90% saturated at P_{AO2} of 60 mm Hg, but the % Hb saturation drops sharply when P_{O2} falls below this level.*

REGULATION OF RESPIRATION DURING EXERCISE

Most important changes during exercise:

- ↑ Respiratory minute volume (↑ ventilation) ⇨ can reach up to 100 L/min depending on the kind and intensity of the exercise.
- ↑ Respiratory rate. The normal respiratory rate is 12 breaths per minute, but during exercise it can reach up to 40-50/min, and V_T can reach the FVC = 4.6 L (you inspire maximally and expire maximally).
- ↑ Ventilation, the most important change during exercise ⇨ ↑ air reaching alveoli for gas exchange.
- ↑ O_2 consumption (O_2 uptake). The normal O_2 consumption is 250 ml/min, but during exercise it can reach up to 20 times as much (2.5 L/min).

❑ *In strenuous exercise, oxygen consumption and carbon dioxide formation can increase as much as 20-fold. Yet, in the healthy athlete, alveolar ventilation ordinarily increases almost exactly in step with the increased level of metabolism. Therefore, the arterial P_{O2}, P_{CO2}, and pH remain almost exactly normal.*

Regulation of hyperventilation (most important change during exercise):

① Psychological factor from the cerebral cortex.
② Proprireceptors are active during exercise and increase ventilation. (↑RR)
③ Increase body temperature due to increase metabolism. (↑RR)
④ Muscles of contraction ⇨ produce H^+ ⇨ stimulate the peripheral chemoreceptors.
⑤ Chemical factors (↑P_{CO2}, ↑H^+, ↑P_{O2}) ⇨ this has the *least* affect on hyperventilation.
⑥ Epinephrine, norepinephrine + ↓ P_{CO2} + lactic acid . (↑RR)

Factors that increase O_2 consumption:

① ↑ Alveolar ventilation ⇨ due to:
   a. An increase in the tidal volume.
   b. An increase in the respiratory rate.
② ↑ Capillary blood flow (perfusion, Q) ⇨ due to:
   a. Dilation of pulmonary capillaries.
   b. Opening of dormant closed pulmonary capillary ⇨ ↑ exchange of gases.
   c. ↑ Pulmonary blood pressure (because of ↑ C.O.) ⇨ forces more blood to enter the pulmonary capillary.
③ Both ① and ② cause an increase in V_A/Q ratio.

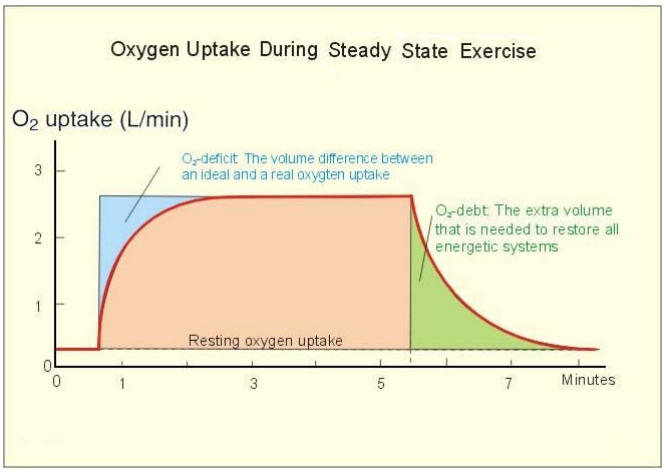
Oxygen Uptake Before, During, and After Exercise:

❶ **Oxygen deficient**: It is the extra amount of O_2 required by the body at the beginning of exercise.

- The energy expended here is greater than the oxygen consumed.
- The extra energy comes from anaerobic metabolism using stored ATP in the body, forming lactic acid.

❷ **Oxygen debt**: It is the extra amount of O_2 used by the body at the end of exercise.

- Hyperventilation persists even after exercise because the extra amount of oxygen is used to:
  1. Convert **lactic acid** back to **glucose**.
  2. Convert **ADP** back to **ATP**.
  3. Return **body temperature** back to normal.
  4. **Creatine phosphate** to its normal state.
- Oxygen consumption does not return to normal levels immediately after exercise but slowly.
- The greater the O_2 debt, the less the fitness & the longer it takes for O_2 levels to return to normal.



✺ **Note**: The sudden increase in O_2 consumption at the beginning of exercise and the sudden decrease in O_2 consumption at the end of exercise are due to the **psychological factor** in the *cerebral cortex*.

DIFFUSING CAPACITY OF RESPIRATORY MEMBRANE

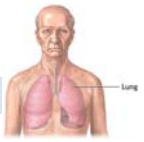
❑ It is the volume of gas which diffuses through respiratory membrane per minute per mmHg.

- At rest = 21 mL/min/mmHg.
- During exercise = 65 mL/min/mmHg

PERCENTAGE OF RESPIRATORY GASES AS THEY ENTER AND LEAVE THE LUNG

Gases	*Atmosphere*	*Alveolar Air*	*Expired Air*	
O_2	20.84%	13.6%	15.7%	⇨ Increase in expired O_2 is due to *more* O_2 in dead space air.
CO_2	0.04%	5.3%	3.6%	⇨ Decrease in expired CO_2 is due to *less* CO_2 in dead space air.

❑ Expired air is used for mouth-to-mouth breathing during pulmonary resuscitation. The oxygen in the expired air is in adequate amounts for respiration while the carbon dioxide in the expired air stimulates the respiratory center.



Role of Respiratory System in Acid-Base Balance

- The respiratory system controls the levels of CO_2 and thus the H^+ concentration in the blood.
- Changes in pH due to the respiratory system are called **respiratory acidosis** or **alkalosis**, while changes in pH due to factors outside the lung are called metabolic acidosis or alkalosis.
  - Respiratory acidosis can be due to hypoventilation because CO_2 remains in the lungs
    ⇨ (↑ H^+, ↓pH).
  - Respiratory alkalosis can be due to hyperventilation because CO_2 leaves the lungs
    ⇨ (↓ H^+, ↑pH):
    - It can be done voluntarily.
    - It may develop after exercise.
    - It may cause tetany due to Ca^{2+} deficiency[1].
  - ***Metabolic acidosis*** (e.g., in increase lactic acid during exercise or accumulation of ketone bodies in diabetes mellitus), can be corrected by hyperventilation.
  - ***Metabolic alkalosis*** (e.g., chronic vomiting & diarrhea), and can be corrected by hypoventilation.

- **Note**: Alkalosis and acidosis are also corrected by the kidneys.
- During ***Metabolic Alkalosis***, respiratory center is **inhibited** leading to **hypoventilation**
  ⇨ ↑ H^+ (correct pH)
- During ***Metabolic Acidosis***, chemoreceptors are **stimulated** leading to **hyperventilation**
  ⇨ ↓ H^+ (correct pH)

Respiratory Insufficiency – Pathophysiology, diagnosis, O_2 Therapy

Normal Range of Arterial Gases at Sea Level

① **P_{AO2}** = 85 – 95 mm Hg. ⇨ P_{AO2} ↓ 85 mm Hg indicate **hypoxia**.

② **P_{ACO2}** = 35 – 48 mm Hg ⇨ P_{ACO2} ↑ 48 mm Hg causes **hypercapnia**.

⇨ P_{ACO2} ↓ 35 mm Hg causes **hypocapnia**.

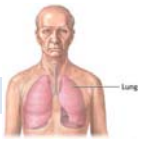
③ **pH** = 7.33 – 7.45 ⇨ ↑ 7.45 is called **alkalemia** (alkalosis).

⇨ ↓ 7.33 is called **acidemia** (acidosis).

④ **S_{AO2}** = 94 – 98% (arterial O_2 saturation).

⑤ **HCO_3^a** = 23 – 28 mEq/L.

[1] *To see how this occurs, refer to* ***Endocrine Physiology; Calcium in Plasma and Interstitial Fluid****, page 16.*



HYPOXIA

- *Definition*: It is an inadequate O_2 supply to the tissues, or the inability of O_2 to be utilized by the tissues.
- *Factors causing hypoxia*:

1) **Decreased oxygenation of the blood in the lungs**:

a. Extrinsic causes:

❶ Deficiency of oxygen in the atmosphere (e.g., high altitudes).

❷ Hypoventilation due to neuromuscular disorders (dysfunction of muscles of respiration, such as paralysis of the respiratory muscles, kyphosis, and scoliosis).

b. Intrinsic causes (pulmonary disease):

❶ Hypoventilation due to increased airway resistance (e.g., asthma) or decreases pulmonary compliance.

❷ Abnormal V_A/Q – alveolar ventilation-perfusion ratio, (e.g., increased physiological dead space or increased physiological shunt such as a pulmonary embolism).

❸ Impairment or abnormality of the respiratory membrane due to increased thickness (e.g., pulmonary edema) or decreased surface area (e.g., emphysema).

2) **Decreased transport of oxygen by the blood to the tissues**:

① Anemia or abnormal hemoglobin (e.g., sickle cell disease) ⇨ *anemic hypoxia*.

② Generalized impairment of the circulation (e.g., hypovolemic shock, ↓ BP, ↓ C.O.) ⇨ *stagnant hypoxia*.

③ Localized impairment of the circulation (e.g., coronary & cerebral vessel obstruction causing ischemia).

④ Tissue edema (increased interstitial fluid causing a decrease in O_2 transport to the tissues).

⑤ Interarterial septal defect ("right-to-left" cardiac shunts): deoxygenated blood goes from right atrium to left atrium, decreasing oxygen delivery.

3) **Decreased tissue capability of using oxygen**:

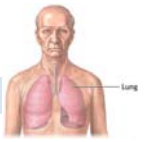
- *Histotoxic hypoxia* (e.g., cyanide poisoning): cyanide inhibits the action of the enzyme *cytochrome oxidase*, so that tissues cannot use O_2 even when plenty is available.

- *Effects of hypoxia on the body*:

- Hypoxia, if sever enough, can cause death of cells throughout the body, but in less sever degrees it causes:
  (1) Depressed mental activity, sometimes culminating in coma.
  (2) Reduced work capacity of the muscles.

- *Oxygen therapy* (i.e., breathing pure oxygen) *for hypoxia*:

- Types of hypoxia where oxygen therapy is *extremely effective*:
  - Atmospheric hypoxia.
  - Hypoventilation hypoxia.
  - Hypoxia caused by impaired alveolar membrane diffusion.
- Types of hypoxia where oxygen therapy is only of *little benefit*:
  - Anemic hypoxia (hypoxia caused by anemia and abnormal hemoglobin transport of oxygen).
  - Circulating deficiency.
  - Physiological shunt.
- Types of hypoxia that *cannot* be treated by oxygen therapy:
  - Hypoxia caused by inadequate tissue use of oxygen (*histotoxic anemia*).



- *Danger of breathing 100% oxygen* (*Oxygen toxicity*):
  ① Bronchopneumonia.
  ② Ischemia to the brain.
  ③ O_2 metabolism leads to the formation of **free radicals** (hydrogen peroxide, superoxide) that can cause severe damage to the tissue.
  ④ In newborns, oxygen levels above 40% can lead to blindness.

Poly unstratified fatty acid (membranes of nervous system) if oxidized by free radicals, can have adverse effects of brain function ⇨ effect CNS. There is an enzyme which inhibits the action of free radicals, known naturally as ***antioxidants***.

☞ **In short**: ↑ P_{O2} ⇨ ↑ soluble O_2 ⇨ ↑ free radicals.

✵ **Note**: ↓ P_{CO2} in systemic circulation ⇨ vasodilation.
↑ P_{CO2} in systemic circulation ⇨ vasoconstriction ⇨ ↓ blood flow to the brain.
↓ P_{CO2} in pulmonary circulation ⇨ vasoconstriction.

CYANOSIS

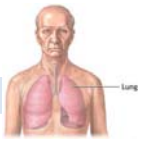
- *Definition*: It is the bluish coloration of the skin, and appears mostly on the lips, tongue, and nail beds.
- *Cause*: appears whenever arterial blood contains more than **5 gm of deoxygenated Hb/dL**.

✵ **Note**: A person with *anemia* can never become cyanotic because not enough hemoglobin is available for deoxygenating, and will die before signs of cyanosis appear. In contrast, in a person with *polycythemia vera*, the excess hemoglobin that can become deoxygenated can lead to cyanosis, even under normal conditions.

ADAPTATION TO LOW BAROMETER PRESSURE (HIGH ALTITUDES)

- The normal P_{O2} at sea level is about 159 mm Hg, and the barometric pressure is 760 mm Hg (0 atm).
- P_{O2} decreases when rising above sea level as the barometric pressure falls, this is the basic cause of hypoxia problems at high altitudes. However, the concentration of O_2 remains the same.
- Acute effects of hypoxia at high altitudes (*unacclimatized person*): *drowsiness*, *lassitude*, *mental & muscle fatigue*, *decreased mental proficiency*, *headaches*, *nausea*, *euphoria*, *seizures*, followed by *coma*, and *death*.
- **Mechanisms of adaptation** (i.e. *acclimatization to high altitudes*):

1) Hyperventilation (↓P_{O2} ⇨ stimulation of peripheral chemoreceptors).
2) ↑ RBCs & Hb conc. to transport more oxygen (↑ Erythropoietin by kidneys ⇨ *secondary polycythemia*).
3) ↑ Diffusing capacity of the respiratory membrane, caused by:
   a. ↑ Lung volume du to ↑ size of alveoli.
   b. ↑ Pulmonary blood pressure.
4) ↑ Tissue vascularity (↑ blood to tissues ⇨ ↑ oxygen supply), caused by:
   a. ↑ Size of capillaries.
   b. ↑ Number of capillaries.
5) ↑ Utilization of O_2 by the tissues, caused by:
   a. ↑ Mitochondria.
   b. ↑ Myoglobin (transports O_2 from the muscle membrane to mitochondria and has a higher affinity for O_2 than hemoglobin)
   c. ↑ Activity of *cytochrome oxidase* enzyme.
   d. ↑ level of oxidative enzyme.
6) ↑ O_2 delivery to tissues ⇨ oxyhemoglobin curve shifts to right caused by ↑ 2, 3-DPG induced by hypoxia.



❋ **Note**: Although hyperventilation causes a ↓P_{CO2} which increase hemoglobin affinity for oxygen and should shift the oxyhemoglobin curve to the *left*, the affect of ↑ 2, 3 biphosphoglycerate is much stronger than P_{CO2} so that the overall affect is a shift of the oxyhemoglobin curve to the *right*.

Acute Mountain Sickness:

- During the first few hours after rising to a high altitude and up to 8-24 hours, some people can develop **brain edema** (due to local vasodilatation of the cerebral blood vessels ⇨ increase capillary pressure ⇨ causes fluid to leak into the cerebral tissues), symptoms include:
  - Headache.
  - Irritability.
  - Vomiting.
  - Loss of focus (disorientation).
- Adaptation to high altitudes (acclimatization) often occurs after 24 hours, and symptoms subside.
- Pulmonary edema (high altitude + physical work) → hypoxia → vasoconstriction in some parts of the pulmonary circulation → fluid goes to less constricted areas → localized edema.

High Gas Pressure

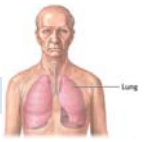
The atmospheric pressure increases by one atmospheric pressure (760 mm Hg) for every 10 m (33 ft) below sea level, which means for every 10 m (33 feet) below sea level, barometric pressure will double.

> ❑ *If a diver descends 10 meters below sea level, therefore, the partial pressure and amounts of dissolved gases in the plasma will be twice those values at sea level. At 20 meters, they are three times, and at 30 meters they are four times the value of sea level. The increased amount of nitrogen and oxygen dissolved in the blood plasma under these conditions can have serious effects on the body.*

At high pressures, the lungs will collapse. This can be avoided by applying oxygen under high pressures to counter the effect of the high barometric pressure.

> ❑ *Due to the dangers of oxygen toxicity from breathing 100% oxygen or when P_{O2} raises above 2.5 atm (1900 mm Hg), deep-sea divers commonly use gas mixtures in which oxygen is diluted with inert gases such as nitrogen (in ordinary air) or helium.*

Applying gases under high pressure will increase the absorption of all gases. The increase of O_2 and CO_2 absorption within limits is not toxic, but the increase in N_2 absorption can cause the following:



(A) **Decompression Sickness**:

- *Definition*: If a diver has been beneath the sea long enough that large amounts of nitrogen have been dissolved in his or her body and the diver suddenly comes back to surface of the sea, significant quantities of nitrogen bubbles can develop in the body fluids and enter the blood, blocking blood vessels and causing ischemia and sometimes tissue death; this is called **decompression sickness**.
- *Symptoms*: severe pain in the joints and muscles of the legs and arms, disorientation or coma.
- *Prevention and treatment*:

  ① **Rising slowly to the surface**: a large amount of nitrogen will diffuse through the alveoli and be eliminated in the expired breath, preventing decompression sickness.

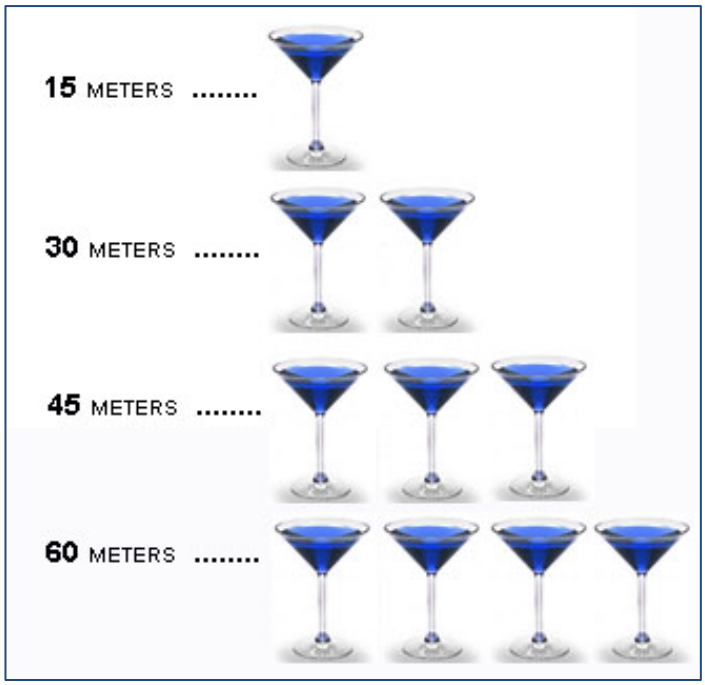
  ② **Putting the diver into a pressurized tank** and then lowering the pressure gradually back to normal atmospheric pressure.

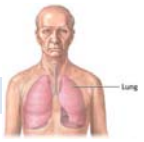
  ③ **Helium-oxygen mixture** instead of a nitrogen-oxygen mixture in the diver's breathing tank: (helium is only $^1/_5$ as narcotic as nitrogen, and slowly, it is less dense than N_2, and it keeps the airway resistance for breathing at a minimum).

❑ Airplanes flying at high altitudes have pressurized cabins so that the passengers do not experience the very low atmospheric pressure of these altitudes. If a cabin were to loose pressure suddenly (e.g., broken window or open cabin door), people in this situation, like the divers that ascend too rapidly, would experience decompression sickness.

(B) **Nitrogen Narcosis**:

- When the diver remains beneath the sea for an hour or more and is breathing high-pressure air, symptoms of narcosis begin to appear, such as: *euphoria*, *drowsiness*, *weakness*, and *clumsiness*.
- Mechanism: large amounts of nitrogen dissolve in the fatty substances in the membranes of neurons ⇨ altering ionic conductance through the membranes ⇨ reducing neuronal excitability.
- While the mechanism of the narcotic effect of nitrogen resembles that of gas anesthetics, its characteristics resemble that of *alcohol intoxication*.





Energy Source During Exercise

1. **ATP**: produced in mitochondria.
2. **Creatin phosphate (CP)**: CP + ADP ⇨ ATP + creatin.
   ⇨ CP is broken down in muscles to form ATP.
3. **Anaerobic energy:**
   a. **Glucose in blood**
   b. **Glycogen**
   ⇨ More lactic acid (acidosis)
4. **Aerobic energy:** use of O_2 (excess amount of ATP, more than anaerobic).

Types of energy source depend on

1. **Intensity of exercise**
2. **Duration of exercise**
   a. **Short and tough exercise**: anaerobic ATP stored in muscle (CP).
   b. **Aerobic energy**: athletes have big lungs.

Note: ➔ First seconds of exercise, ATP stored is the main source of energy.
➔ During one minute of exercise, you use anaerobic energy.
➔ Using aerobic energy takes hours.

Parameters of physical fitness

1. Increase O_2 consumption ⇨ more fitness:
   ⇨ One liter consumption of O_2 leads to utilization of 5 kCal of energy.
2. Decrease heart rate leads to more fitness (low HR after exercise ⇨ more fitness):
   ⇨ Maximum O_2 consumption when HR is flat.
3. Body Temperature:
   ➔ Lean body mass = body weight – fat content,
   ➔ Then O_2 consumption / lean body mass.