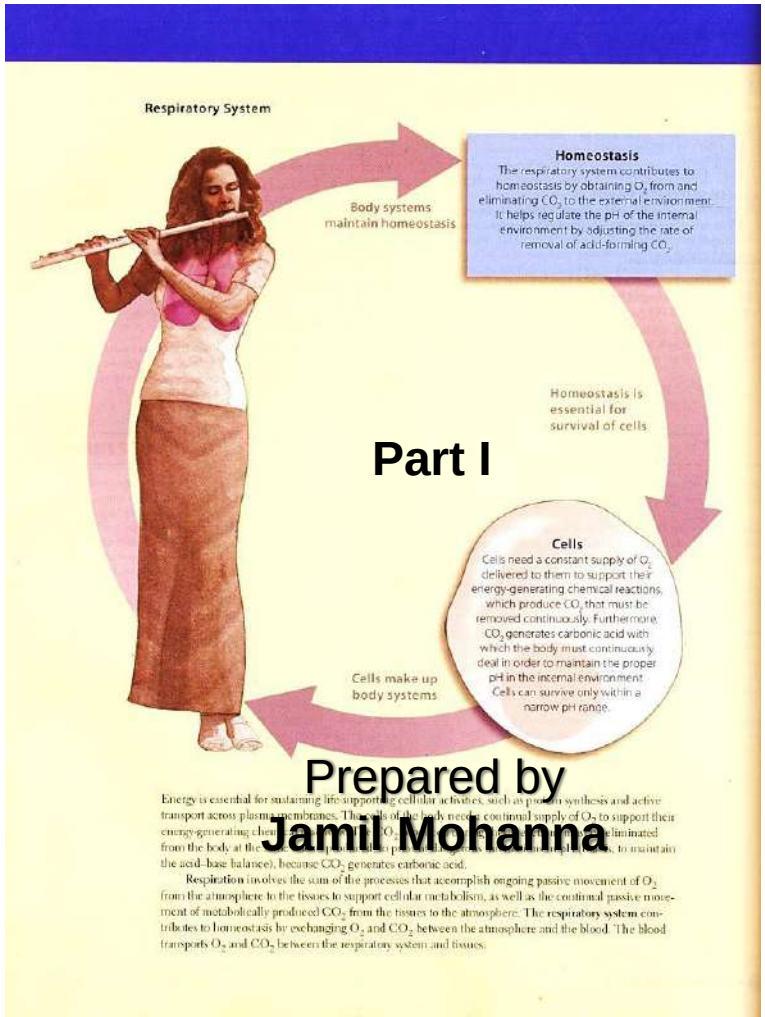
بسم الله الرحمن الرحيم

Chapter 13

The Respiratory System



Part I

Prepared by

Jamil Mohanna

➢Introduction:

- The primary function of respiration is to obtain O_2 for use by the body's cells and to eliminate the CO_2 the cells produce.

The respiratory system does not participate in all steps in respiration

- Respiration encompasses two separate but related processes: *internal and external respiration*

Internal or **cellular respiration**; the intracellular metabolic processes carried out within the mitochondria, which use O_2 and produce CO_2 during derivation of energy from nutrient molecules.

- The **respiratory quotient (RQ)** varies depending on the foodstuff consumed, for CHO is **1** that is, for every molecule of O_2 consumed, one molecule of CO_2 is produced.
- (fat RQ is 0.7 and protein RQ is 0.8).
- On a typical diet consisting of a mixture of these three nutrients;

$$RQ = \frac{CO_2 \text{ produced}}{O_2 \text{consumed}} = \frac{200 \text{ ml/min}}{250 \text{ ml/min}} = 0.8$$

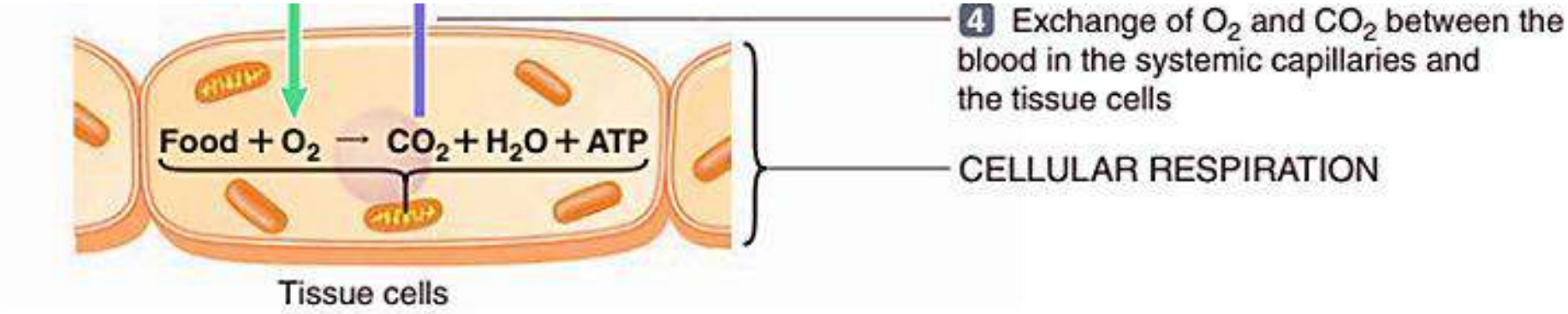
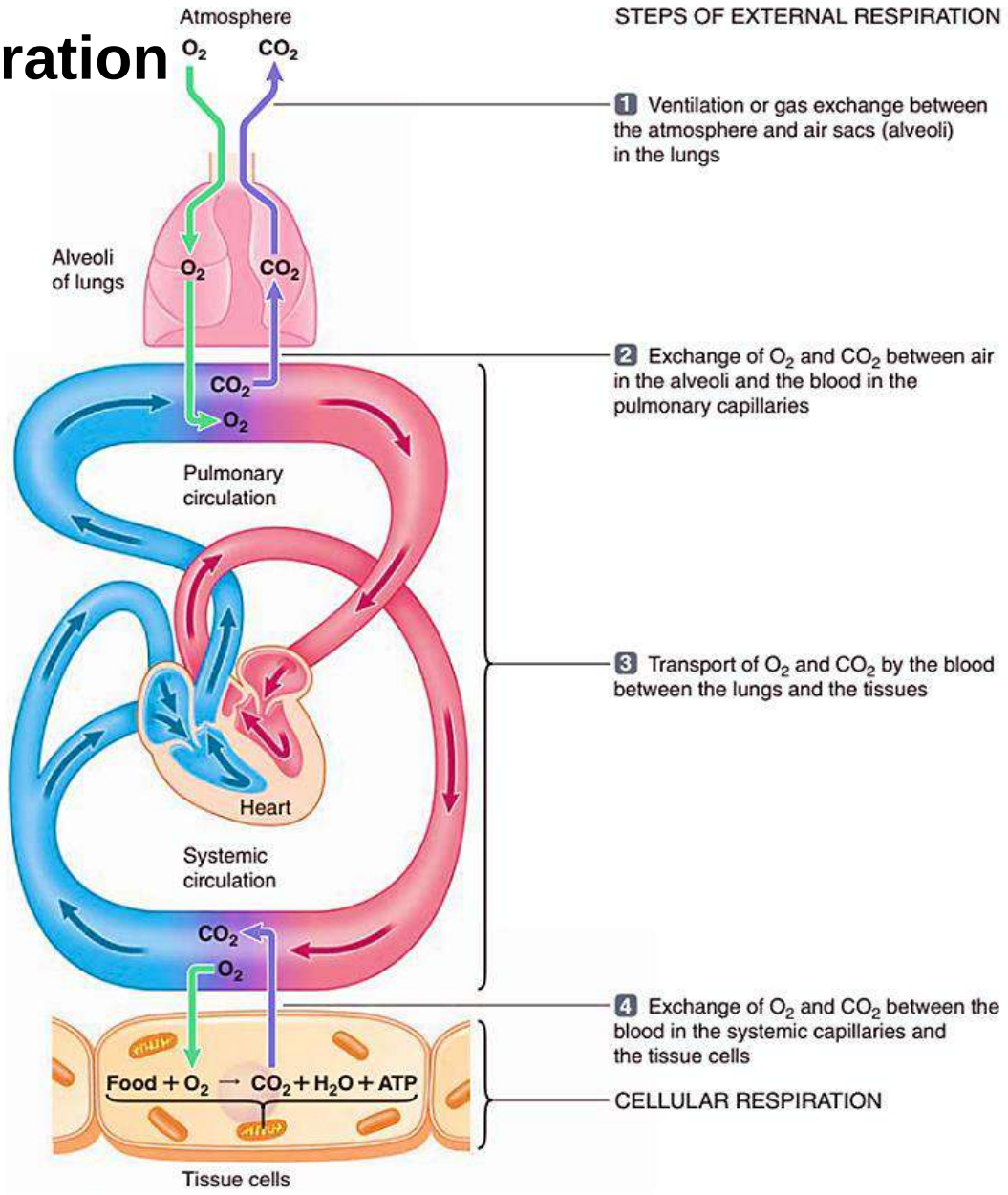


FIGURE 13-1 External and cellular respiration. External respiration encompasses the steps involved in the exchange of O_2 and CO_2 between the external environment and tissue cells (steps 1 through 4). Cellular respiration encompasses the intracellular metabolic reactions involving the use of O_2 to derive energy (ATP) from food, producing CO_2 as a by-product.

External and Internal respiration



● **FIGURE 13-1 External and cellular respiration.** External respiration encompasses the steps involved in the exchange of O_2 and CO_2 between the external environment and tissue cells (steps 1 through 4). Cellular respiration encompasses the intracellular metabolic reactions involving the use of O_2 to derive energy (ATP) from food, producing CO_2 as a by-product.

External respiration:

External respiration refers to the entire sequence of events involved in the exchange of O_2 and CO_2 between the external environment and the cells of the body.

External respiration encompasses four steps **(fig. 13-1)**.

- The respiratory ❶&❷and circulatory systems❸&❹ function together to accomplish external respiration.

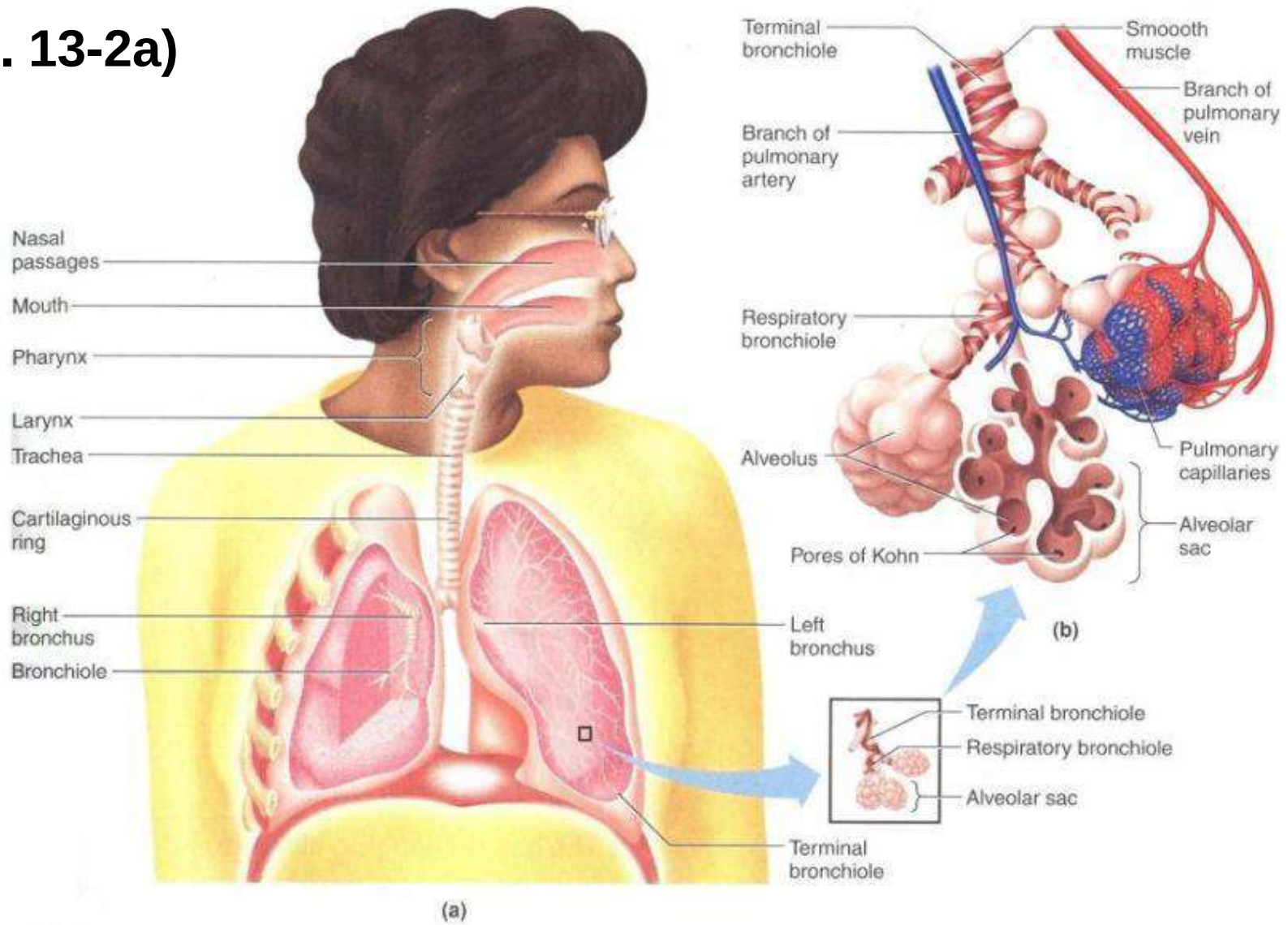
Non-respiratory functions of the respiratory system

- It provides a route for water loss and heat elimination, inspired air is humidified and warmed.
- It enhances venous return.
- It contributes to the maintenance of normal acid-base balance by altering the amount of H^+-generating CO_2 exhaled.
- It enables speech, singing and other vocalization.
- It defends against inhaled foreign matter.
- It removes, modifies, activates, or inactivates various material passing through the pulmonary circulation, e.g. prostaglandins, are *inactivated* during passage through the lungs so that they cannot exert systemic effects. By contrast, the lungs *activate* angiotensin II, a hormone that plays an important role in regulating the concentration of Na^+ in the ECF.
- The nose serves as the organ of smell.

The respiratory airways conduct air between the atmosphere and alveoli

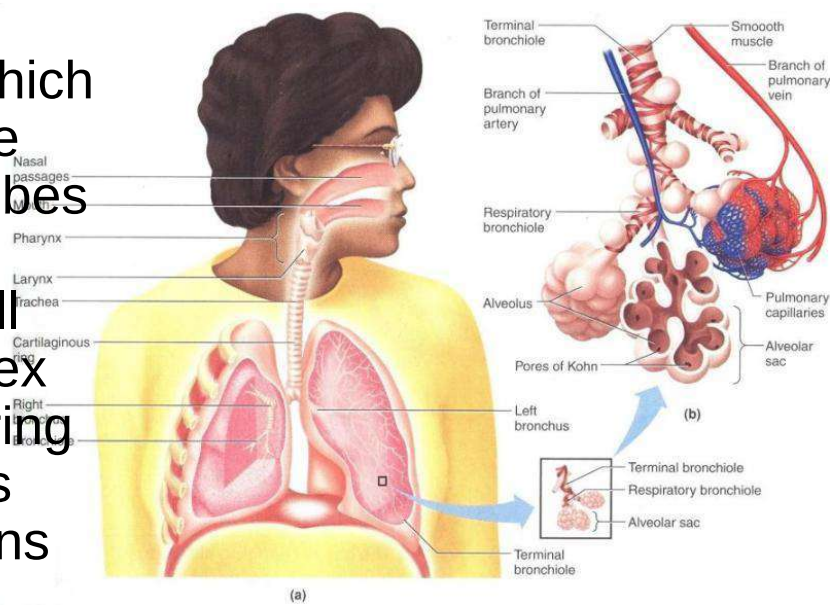
- The **respiratory system** includes ????

(fig. 13-2a)



The respiratory airways conduct air between the atmosphere and alveoli

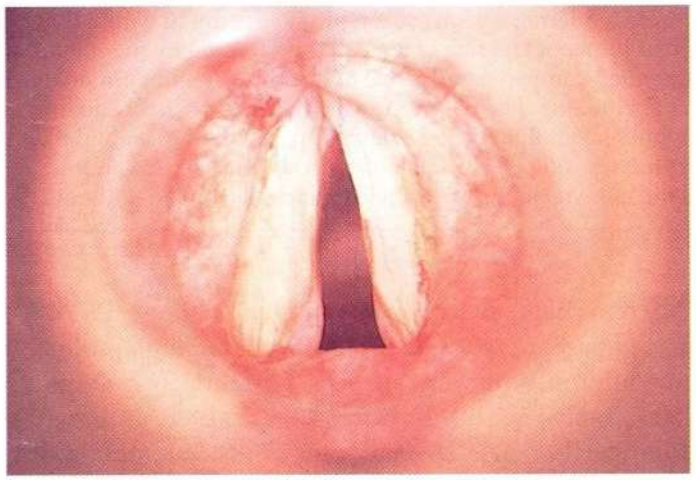
The airways begins with the **nasal passages (nose)** that open into the **pharynx (throat)** which serves as a common passageway for both the respiratory and the digestive systems. Two tubes lead from the pharynx- the **trachea** and the esophagus, air can enter by the mouth as well when the nasal passages are congested, reflex mechanisms exist to close off the trachea during swallowing so that food enters the esophagus and not the airways, so the esophagus remains closed except during swallowing.



The **larynx (vocal box)**, the anterior protrusion of the larynx forms the "*Adam's apple*". The **vocal folds** (**not cords*) two bands of elastic tissue that lie across the opening of the larynx, can be stretched and positioned in different shapes by laryngeal muscles (fig. 13-3). They vibrate to produce the many different sounds of speech.

During swallowing they are brought into tight apposition to each other to close off the entrance of the trachea.

FIGURE 13-3
Vocal folds
Photograph of the vocal folds as viewed from above at the laryngeal opening.



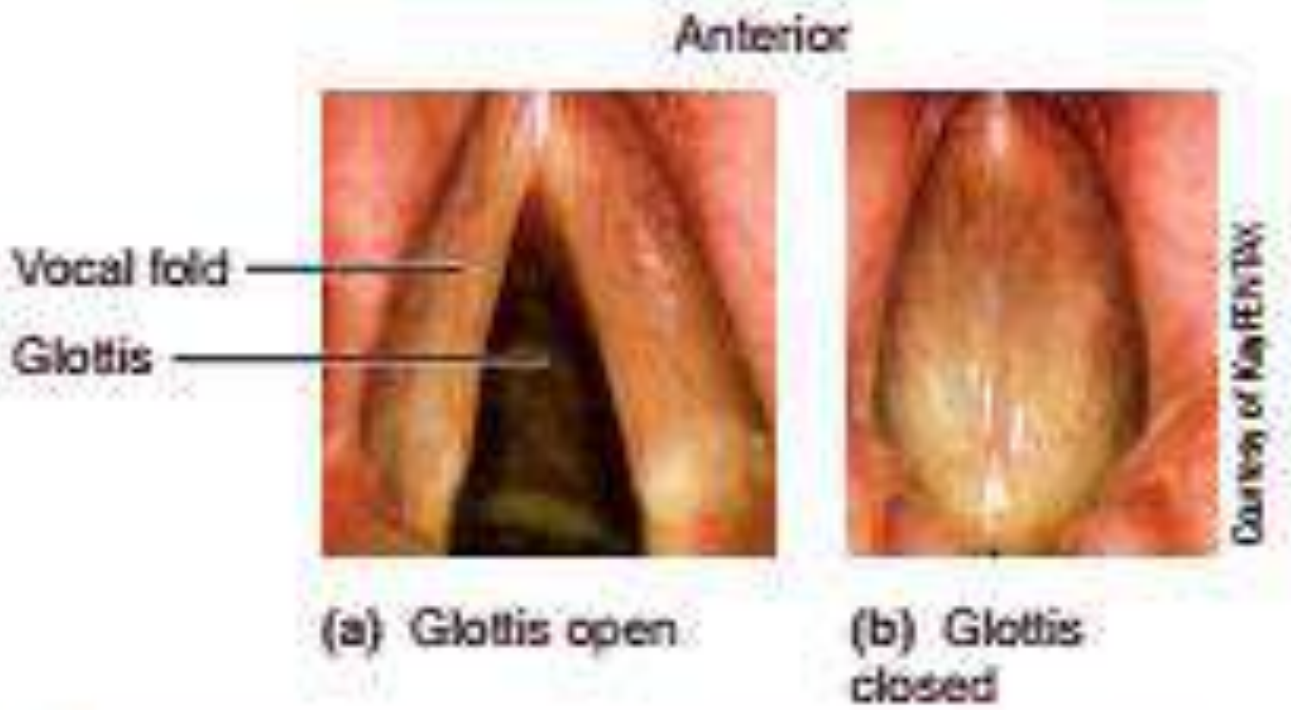
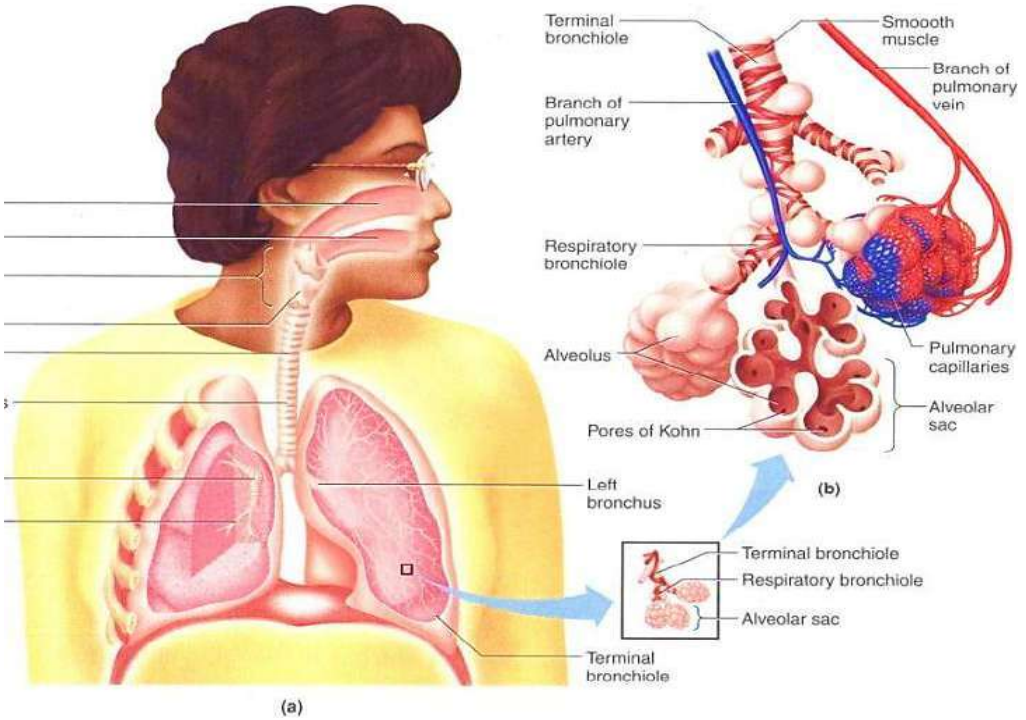
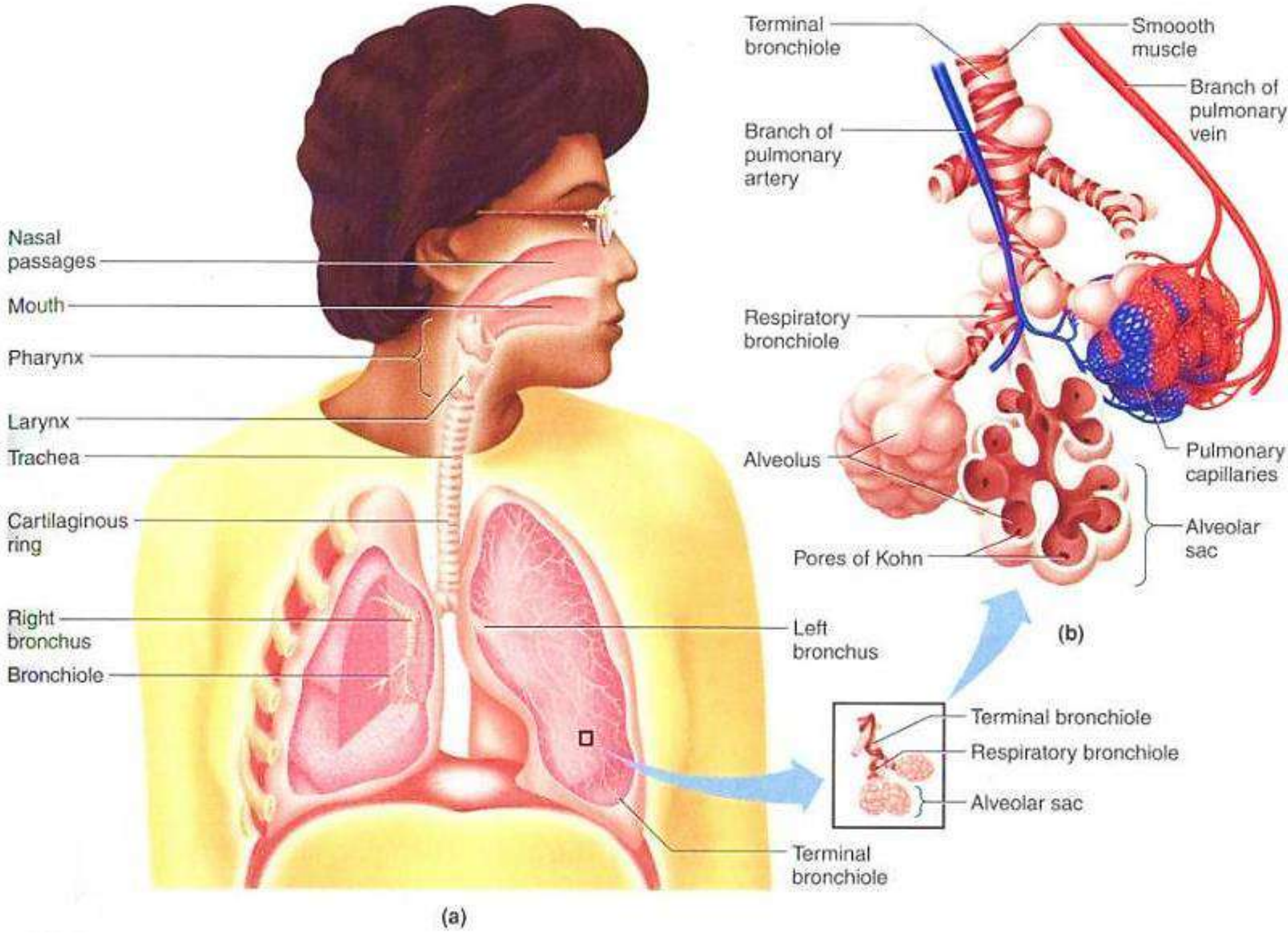


Figure 13-3 Vocal folds. Photographs showing the vocal folds (a) positioned apart when the glottis is open and (b) in tight apposition when the glottis is closed.

- The trachea divides into ***right*** and ***left bronchi***, the bronchus continues to branch into progressively narrower, shorter, and more numerous airways, **bronchioles**. At the ends there are the **alveoli**, the tiny air sacs where gas exchange between air and blood takes palace (fig. 13-2b).
- The trachea and larger bronchi are fairly rigid, non-muscular tubes encircled by a series of cartilaginous rings that prevent these tubes from compressing.
- The smaller bronchioles walls contain smooth muscle that is innervated by the autonomic nervous system and is sensitive to certain hormones and local chemicals, to regulate the amount of air passing between the atmosphere and each cluster of alveoli.




Nasal passages
Mouth
Pharynx
Larynx
Trachea
Cartilaginous ring
Right bronchus
Bronchiole
Left bronchus
Terminal bronchiole
(a)
Terminal bronchiole
Smoooth muscle
Branch of pulmonary vein
Branch of pulmonary artery
Respiratory bronchiole
Alveolus
Pulmonary capillaries
Alveolar sac
Pores of Kohn
(b)
Terminal bronchiole
Respiratory bronchiole
Alveolar sac

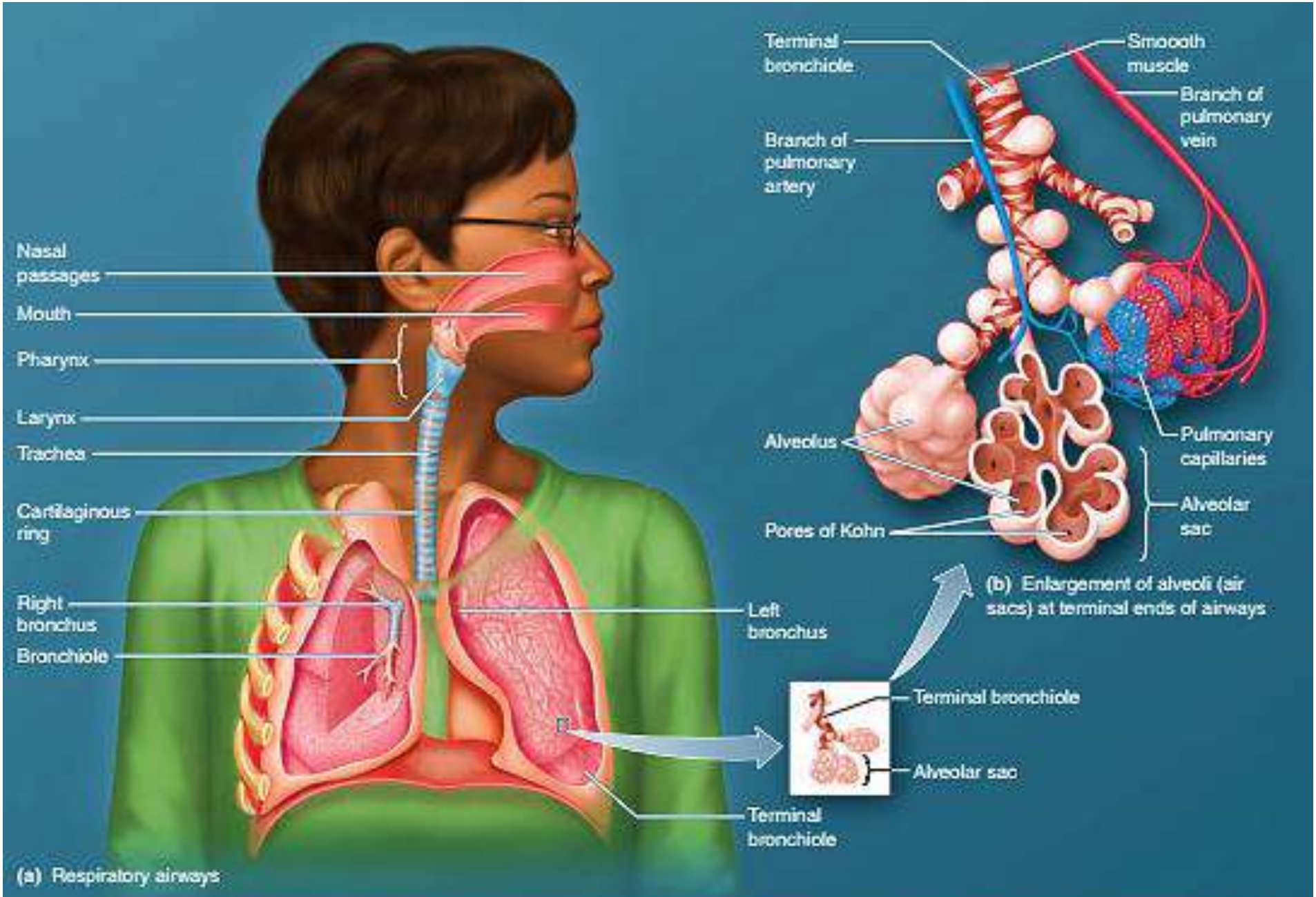
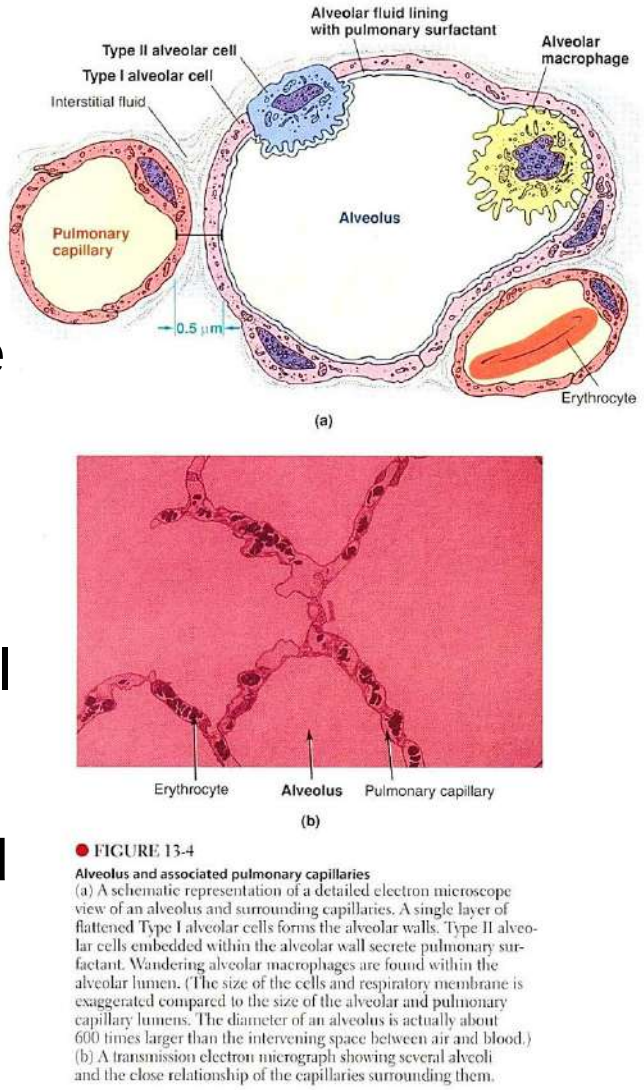


Figure 13-2 Anatomy of the respiratory system. (a) The respiratory airways include the nasal passages, pharynx, larynx, trachea, bronchi, and bronchioles. (b) Most alveoli (air sacs) are clustered in grapelike arrangements at the end of the terminal bronchioles.

The gas-exchanging alveoli are thin-walled, inflatable air sacs encircled by pulmonary capillaries

- Recall that according to **Fick's law** of diffusion, ***the shorter the distance also, the greater the surface area across which diffusion can take place, the greater the rate of diffusion***.

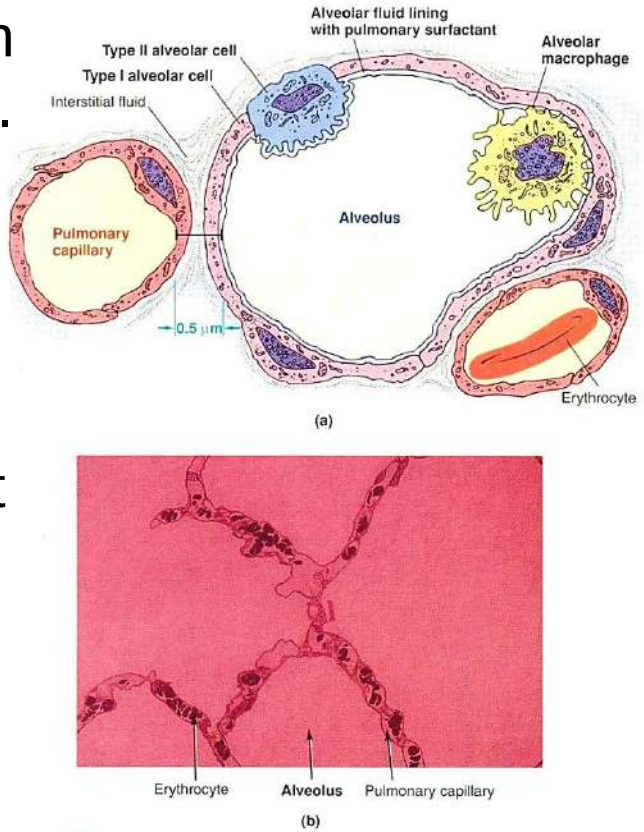
The alveoli are clusters of thin-walled, inflatable, grapelike sacs at the terminal branches of the conducting airways (fig. 13-2b). The alveolar walls consist of a single layer of flattened **Type I alveolar cells** (fig 13-4a). The walls of the dense network of pulmonary capillaries encircling each alveolus are also only one cell thick. The interstitial space forms an extremely thin barrier, with only 0.5 μm separating the air in the alveoli from the blood in the pulmonary capillaries. The thinness of this barrier facilitates gas exchange.



● FIGURE 13-4
Alveolus and associated pulmonary capillaries
(a) A schematic representation of a detailed electron microscope view of an alveolus and surrounding capillaries. A single layer of flattened Type I alveolar cells forms the alveolar walls. Type II alveolar cells embedded within the alveolar wall secrete pulmonary surfactant. Wandering alveolar macrophages are found within the alveolar lumen. (The size of the cells and respiratory membrane is exaggerated compared to the size of the alveolar and pulmonary capillary lumens. The diameter of an alveolus is actually about 600 times larger than the intervening space between air and blood.) (b) A transmission electron micrograph showing several alveoli and the close relationship of the capillaries surrounding them.

The gas-exchanging alveoli are thin-walled, inflatable air sacs encircled by pulmonary capillaries

- So dense are the pulmonary capillary networks that each alveolus is encircled by an almost continuous sheet of blood (fig. 13-4b).
- The total surface area thus exposed between alveolar air and pulmonary capillary blood is about 75m^2.
- **Type II alveolar cells**, secrete *pulmonary surfactant*, a phospholipoprotein complex that facilitates lung expansion. Furthermore, defensive alveolar macrophages are present within the lumen of the air sacs.
- Minute **pores of Kohn** exist in the walls between adjacent alveoli, permits airflow between adjoining alveoli as **collateral ventilation**. (fig. 13-2b)



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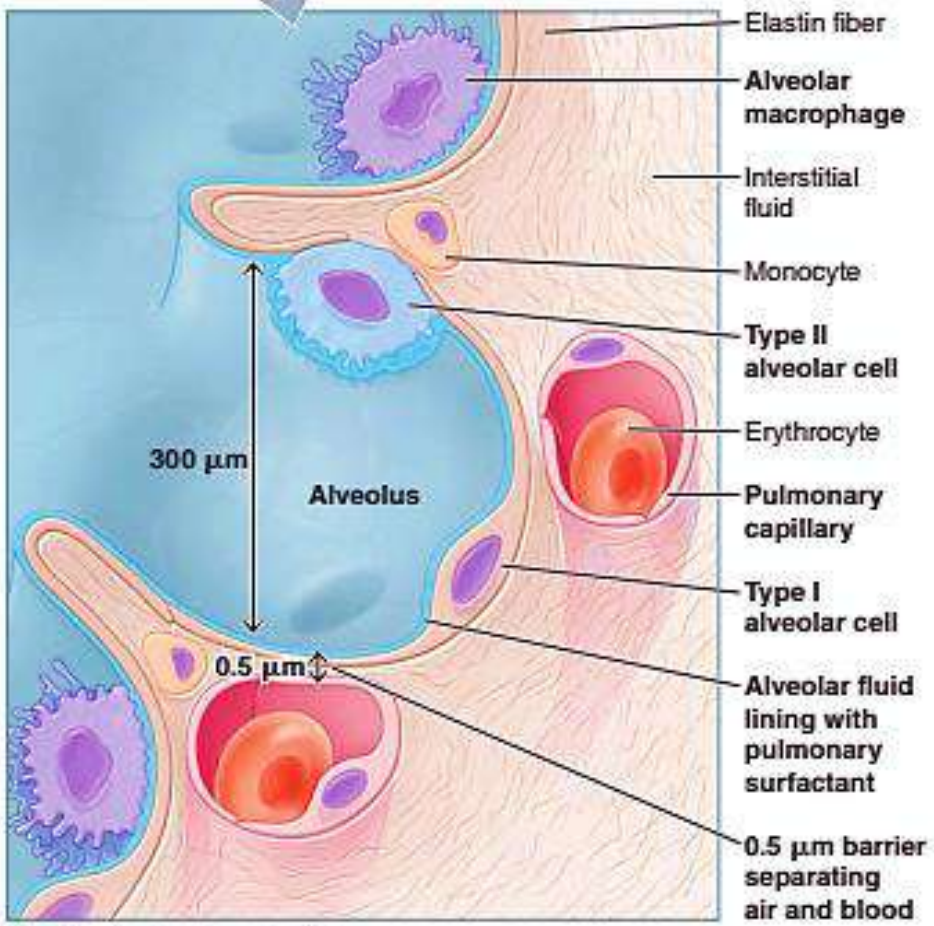
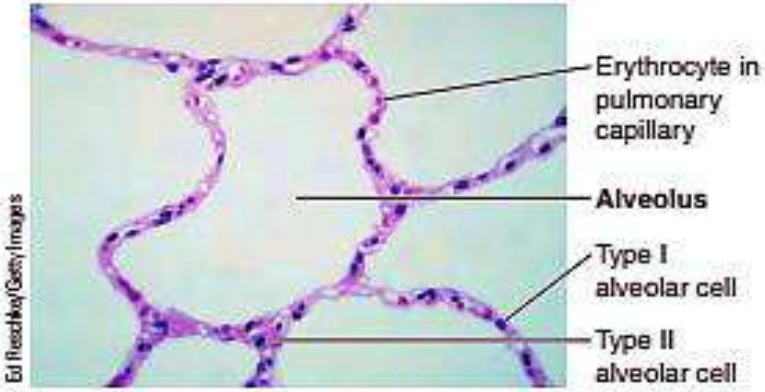
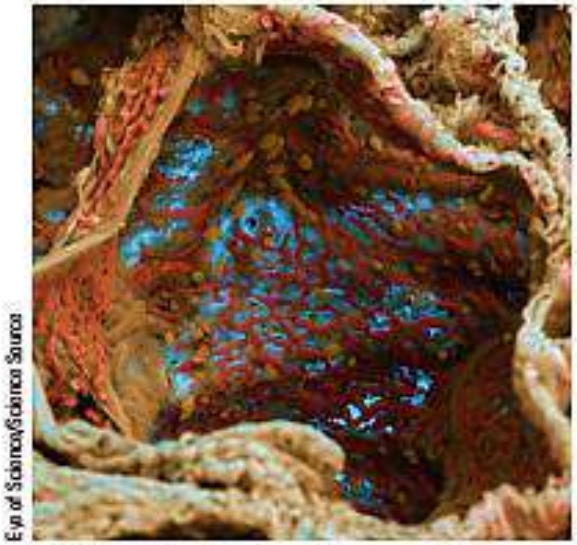
shaped sheet of skeletal muscle that separates the thoracic cavity from the



(a) Alveolus and surrounding pulmonary capillaries



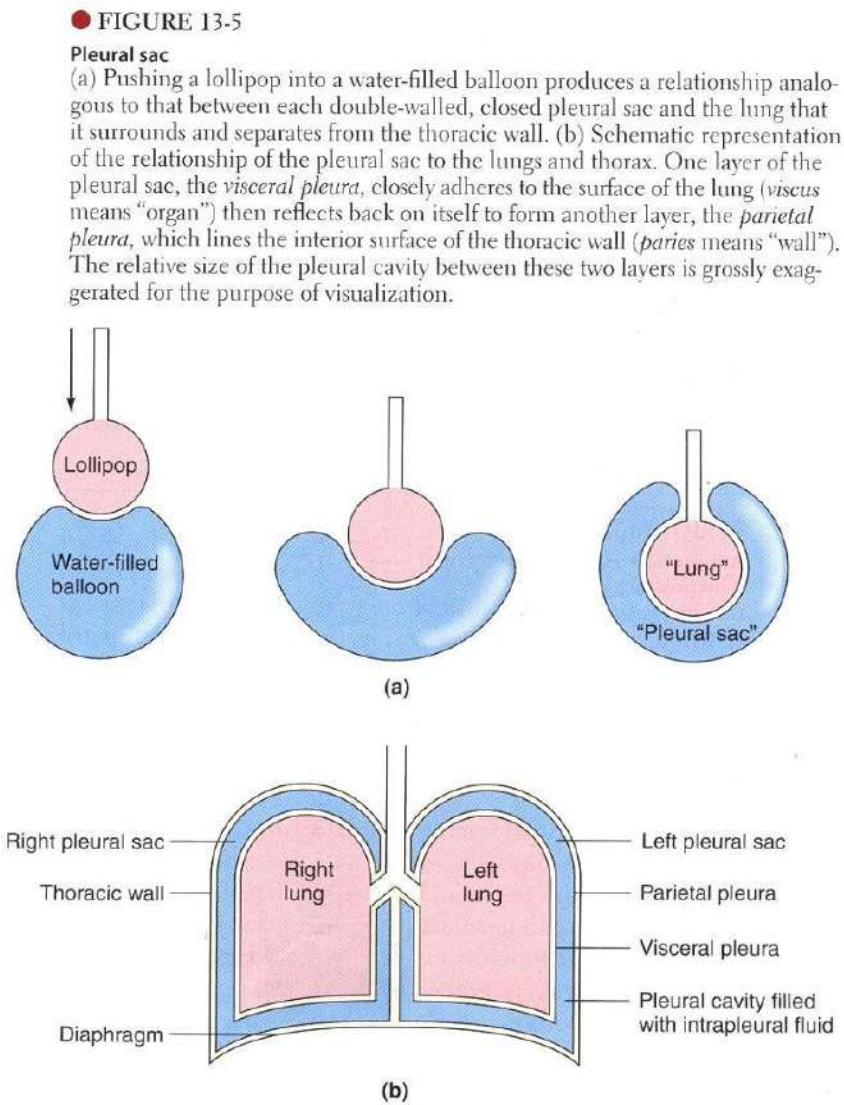
(b) Immunofluorescent photomicrograph of several alveoli



(c) Scanning electron micrograph of a network of pulmonary capillaries surrounding an alveolus cut open for visibility

A pleural sac separates each lung from the thoracic wall

- A double-walled, closed sac called the **pleural sac** separates each lung from the thoracic wall and other surrounding structures (fig. 13-5).
- The surfaces of the pleura secrete a thin **intrapleural fluid**, which lubricates the pleural surfaces as they slide past each other during respiratory movements. **Pleurisy**, an inflammation of the pleural sac, is accompanied by painful breathing, because each inflation and each deflation of the lungs cause a “friction rub”.



The lungs are normally stretched to fill the larger thorax

Two forces hold the thoracic wall and lungs in close apposition, stretching the lungs to fill the larger thoracic cavity

- **Intrapleural fluid's cohesiveness**

The polar water molecules in the intrapleural fluid resist being pulled apart because of their attraction to each other. Tends to hold the pleural surfaces together , can be considered very loosely as a "stickiness" or "glue" between the lining of the thoracic wall and the lung, such as two wet glass slides? But you can pull the slides apart only with great difficulty, because the molecules within the intervening liquid resist being separated. That is, when the thorax expands, the lungs being stuck to the thoracic wall by virtue of the intrapleural fluid's cohesiveness.

- **Transmural pressure gradient**

The intra-alveolar pressure is greater than the intrapleural pressure of 756 mm Hg, so a greater pressure is pushing outward than is pushing inward across the lung wall, pushes out on the lungs, stretching, or distending them (fig. 13-8), the lung are always forced to expand to fill the thoracic cavity.

A similar transmural pressure gradient exist across the thoracic wall, the highly distensible lungs are influenced by this modest pressure differential to a much greater extent than the more rigid thoracic wall is.

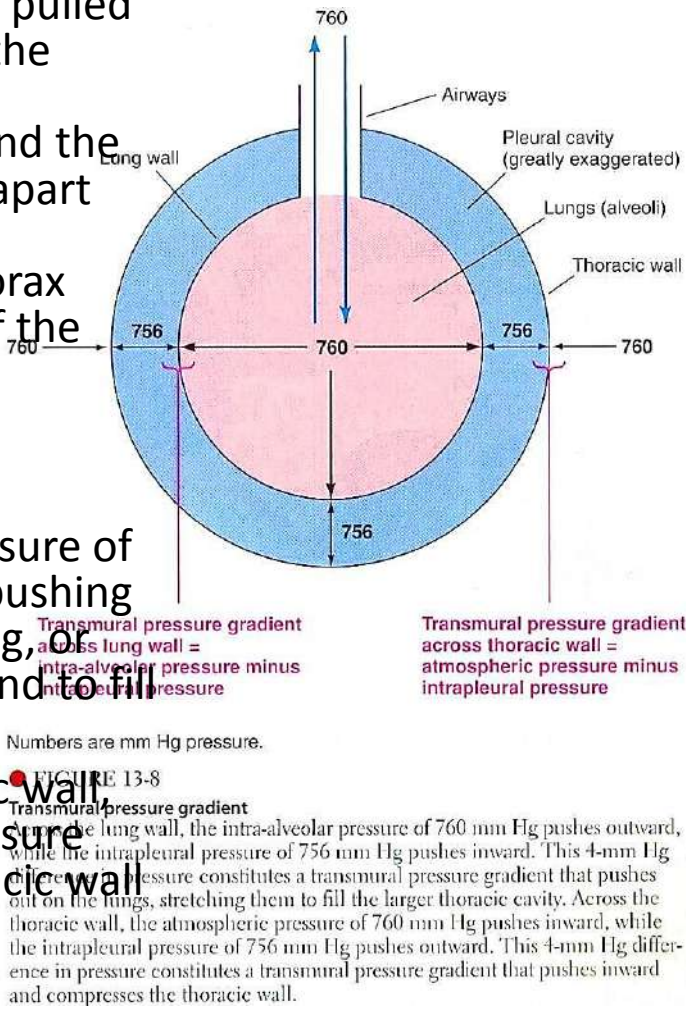


FIGURE 13-8
Transmural pressure gradient
Across the lung wall, the intra-alveolar pressure of 760 mm Hg pushes outward, while the intrapleural pressure of 756 mm Hg pushes inward. This 4-mm Hg difference in pressure constitutes a transmural pressure gradient that pushes out on the lungs, stretching them to fill the larger thoracic cavity. Across the thoracic wall, the atmospheric pressure of 760 mm Hg pushes inward, while the intrapleural pressure of 756 mm Hg pushes outward. This 4-mm Hg difference in pressure constitutes a transmural pressure gradient that pushes inward and compresses the thoracic wall.

Elastic behavior of the lungs is due to elastic connective tissue and alveolar surface tension

- The lungs can be stretched to varying degrees during inspiration and then recoil to their preinspiratory size during expiration because of their elastic behavior.

1- The term ***pulmonary compliance*** refers to the dispensability of the lungs – how much they stretch in response to a given change in the transmural pressure gradient, the stretching force exerted across the lung wall.

2- The term ***elastic recoil*** refers to the phenomenon of the lungs snapping back to their resting position during expiration.

Specifically, compliance is a measure of the magnitude of change in lung volume accomplished by a given change in the transmural pressure gradient, the force that stretches the lungs.

The lower the compliance of the lungs, the larger the transmural pressure gradient that must be created during inspiration to produce normal lung expansion.

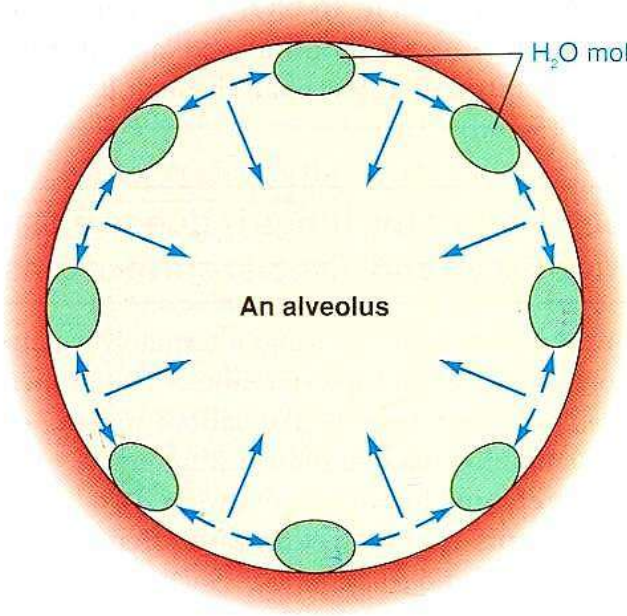
Lacking normal stretchability can be decreased by a number of factors, as in *pulmonary fibrosis*, where normal lung tissue is replaced with scar-forming fibrous connective tissue as a result of chronically breathing asbestos fibers or similar irritants.

Pulmonary elastic connective tissue

- Pulmonary elastic behavior depends on the elastic connective tissue meshwork within the lungs.

Alveolar surface tension

- Which is due to the attractive forces between the surface water molecules in the liquid film lining each alveolus, tends to resist the alveolus being stretched on inflation (decrease compliance) and tends to return it back to a smaller surface area during deflation (increases lung rebound), (fig. 13-16).
- With emphysema, loss of elastin fibers and the reduction in alveolar surface tension resulting the increased airway resistance to the patient's difficulty in expiration.



● FIGURE 13-16

Alveolar surface tension

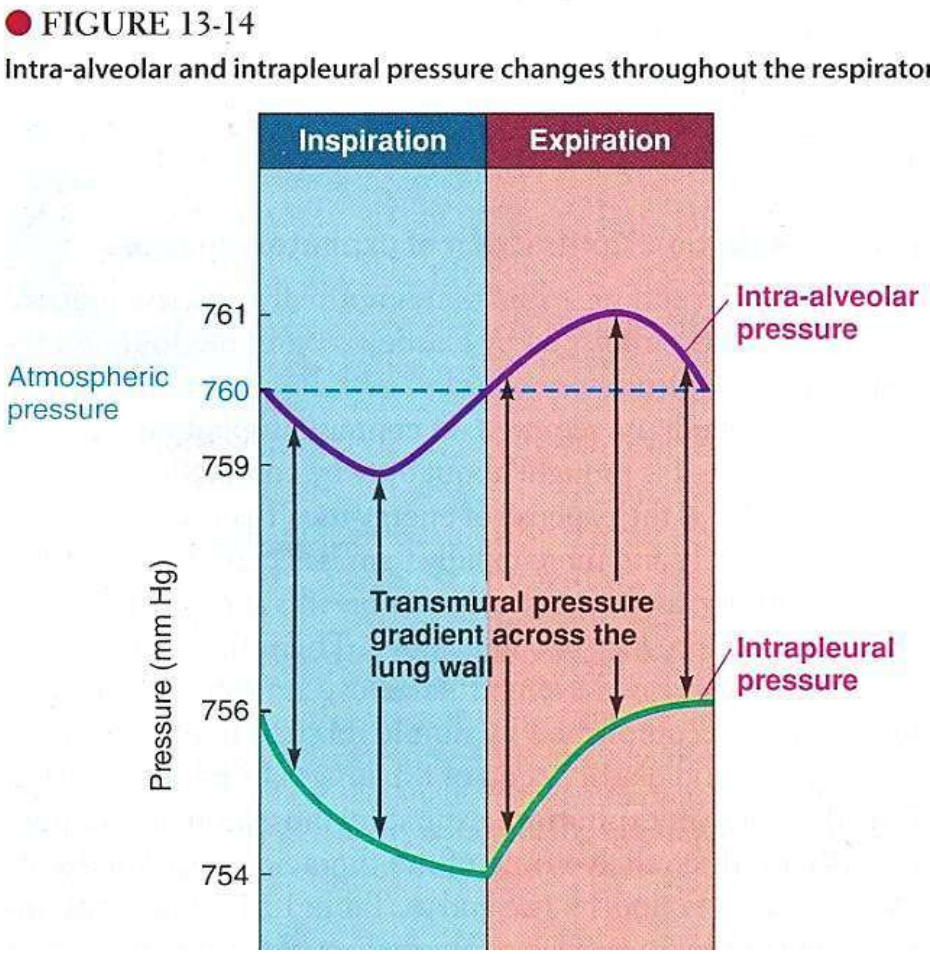
The attractive forces between the water (H_2O) molecules in the liquid film that lines the alveolus are responsible for surface tension. Because of its surface tension, an alveolus (1) resists being stretched, (2) tends to be reduced in surface area or size, and (3) tends to recoil after being stretched.

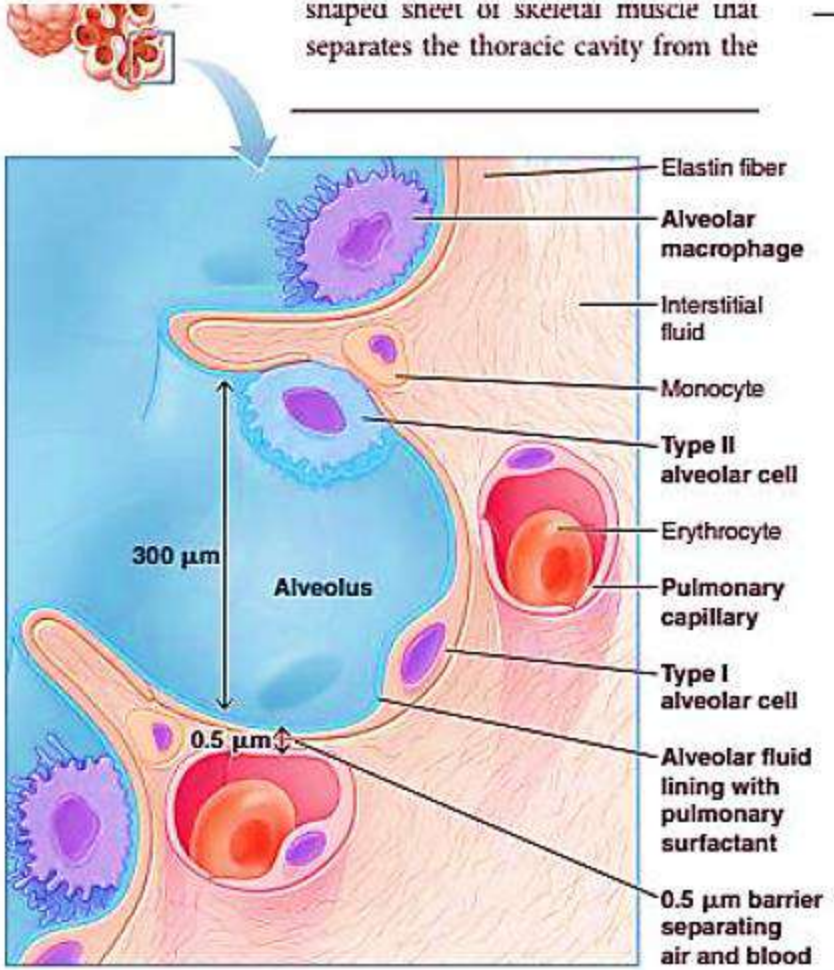
Pulmonary surfactant decreases surface tension and contributes to lung stability

- If the alveoli were lined by water alone, the surface tension would be so great that the lungs would be poorly compliant and would tend to collapse.
- Two factors oppose the tendency for alveoli to collapse , maintaining alveolar stability and reducing the work of breathing;

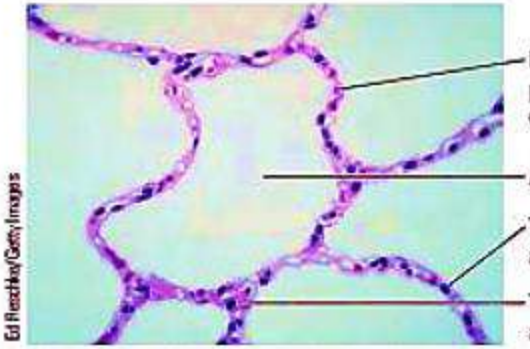
(1) Pulmonary surfactant; a complex mixture of lipids and proteins secreted by the **Type II** alveolar cells, (fig. 13-14a).

- Pulmonary surfactant intersperses between the water molecules and lowers the alveolar surface tension, thereby (1) increasing the compliance of the lungs and (2) counteracting the tendency for alveoli to collapse.

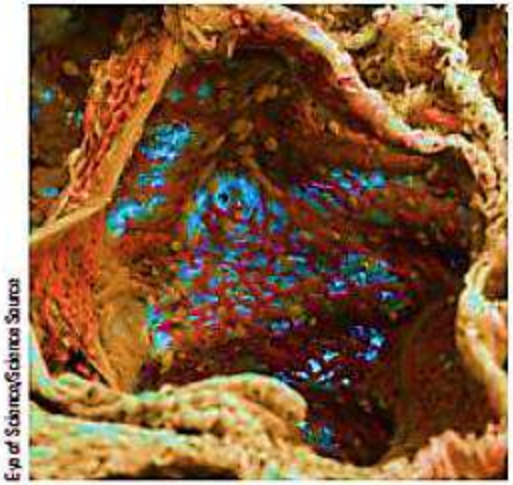




(a) Alveolus and surrounding pulmonary capillaries



(b) Immunofluorescent photomicrograph of several alveoli



(c) Scanning electron micrograph of a network of pulmonary capillaries surrounding an alveolus cut open for visibility

- If you visualize the alveoli as spherical bubbles, according to the **law of LaPlace**, the magnitude of the inward-directed collapsing pressure is directly proportional to the surface tension and inversely proportional to the radius of the bubble:

$$P = \frac{2T}{r}$$

***P* = inward-directed collapsing pressure.**

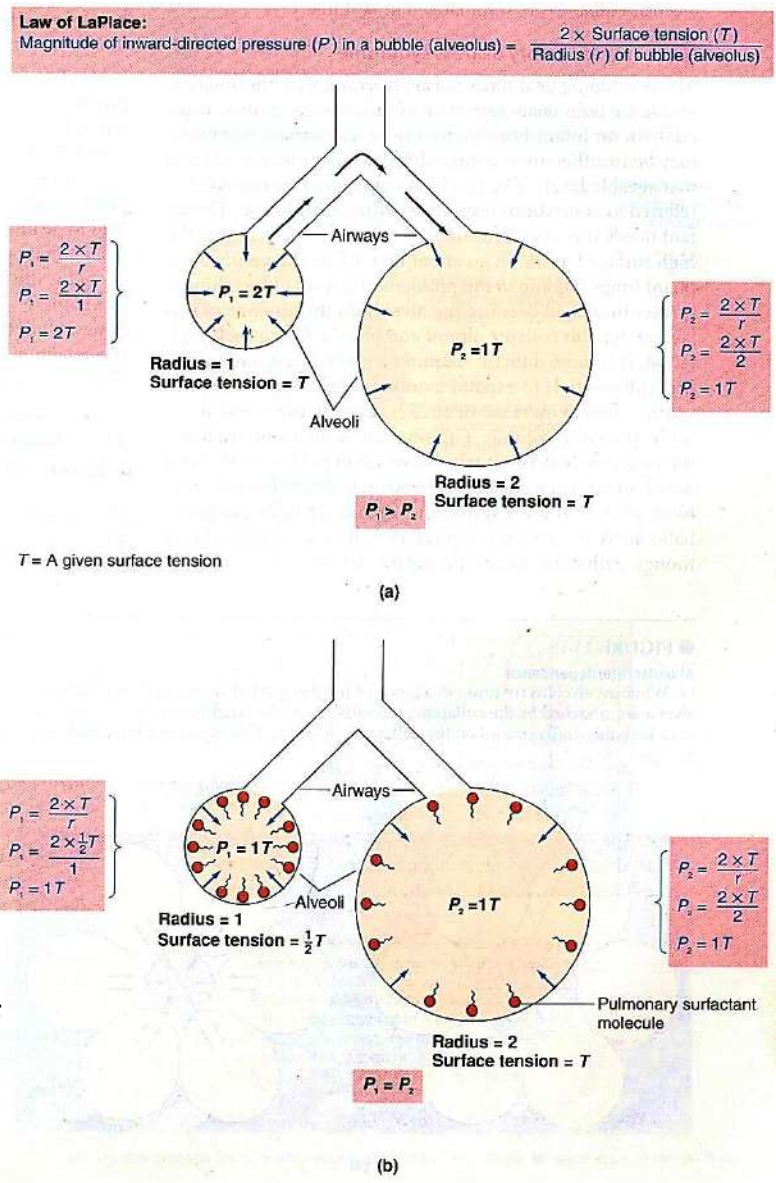
***T* =surface tension.**

***r* = radius of bubble (alveolus).**

So, the smaller its radius and the greater its tendency to collapse at a given surface tension (fig.13-17).

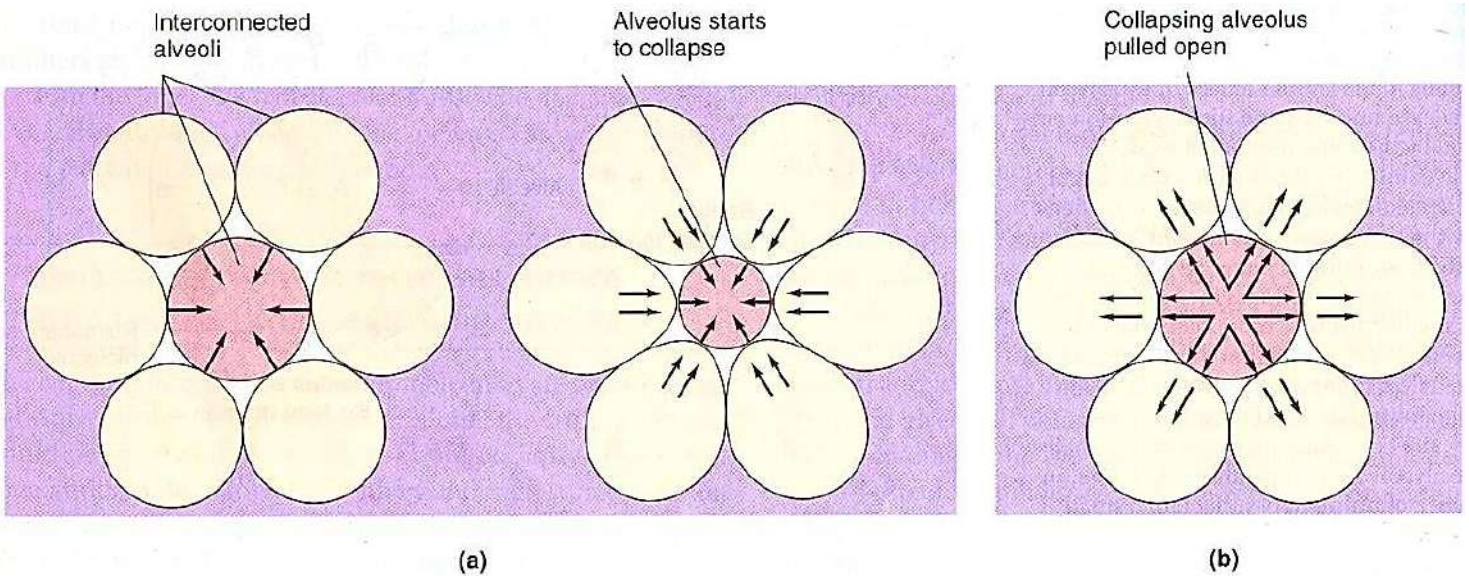
Small alveoli normally do not collapse and blow up larger alveoli, because pulmonary surfactant reduces the surface tension of small alveoli more than that of larger alveoli. Pulmonary surfactant decreases surface tension to a greater degree in small alveoli than in larger alveoli because the surfactant molecules are closer together in the smaller alveoli.

Pulmonary surfactant therefore helps stabilize the sizes of the alveoli and helps keep them open and available to participate in gas exchange.



(2) alveolar interdependence, among neighboring alveoli

- Each alveolus is surrounded by other alveoli and interconnected with them by connective tissue(fig.13—18a).



- The opposing forces acting on the lung (that is, the forces keeping the alveoli open and the countering forces that promote alveolar collapse) are summarize in (table 13-3).

▲ TABLE 13-2 **Opposing Forces Acting on the Lung**

Forces Keeping the Alveoli Open	Forces Promoting Alveolar Collapse
Transmural pressure gradient	Elasticity of stretched pulmonary connective tissue fibers
Pulmonary surfactant (which opposes alveolar surface tension)	Alveolar surface tension
Alveolar interdependence	

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New born respiratory distress syndrome

- When pulmonary surfactant may be insufficient to reduce the alveolar surface tension to manageable levels. The resulting collection of symptoms referred to as **newborn respiratory distress syndrome**
- In the absence of surfactant, tend to collapse almost completely during each expiration. It is more difficult to expand a collapsed alveolus by a given volume than to increase an already partially expanded alveolus by the same volume, *analogous to blowing up a new balloon*.
- Lung expansion may require transmural pressure gradients of 20-30 mm Hg (compared to the normal 4-6 mm Hg), respiratory distress associated with surfactant deficiency may soon lead to death.
- Until the surfactant-secreting cells mature sufficiently, the condition is treated by surfactant replacement. In addition, drugs can hasten the maturation process.

The work of breathing normally requires only about 3% of total energy expenditure

- the respiratory muscles must work during inspiration to expand the lungs against their elastic forces and to overcome airway resistance, whereas expiration is passive. The work of breathing may be increased in four different situations:

1- *When pulmonary compliance is decreased*, such as with pulmonary fibrosis.

2- *When airway resistance is increased*, such as with **COPD**.

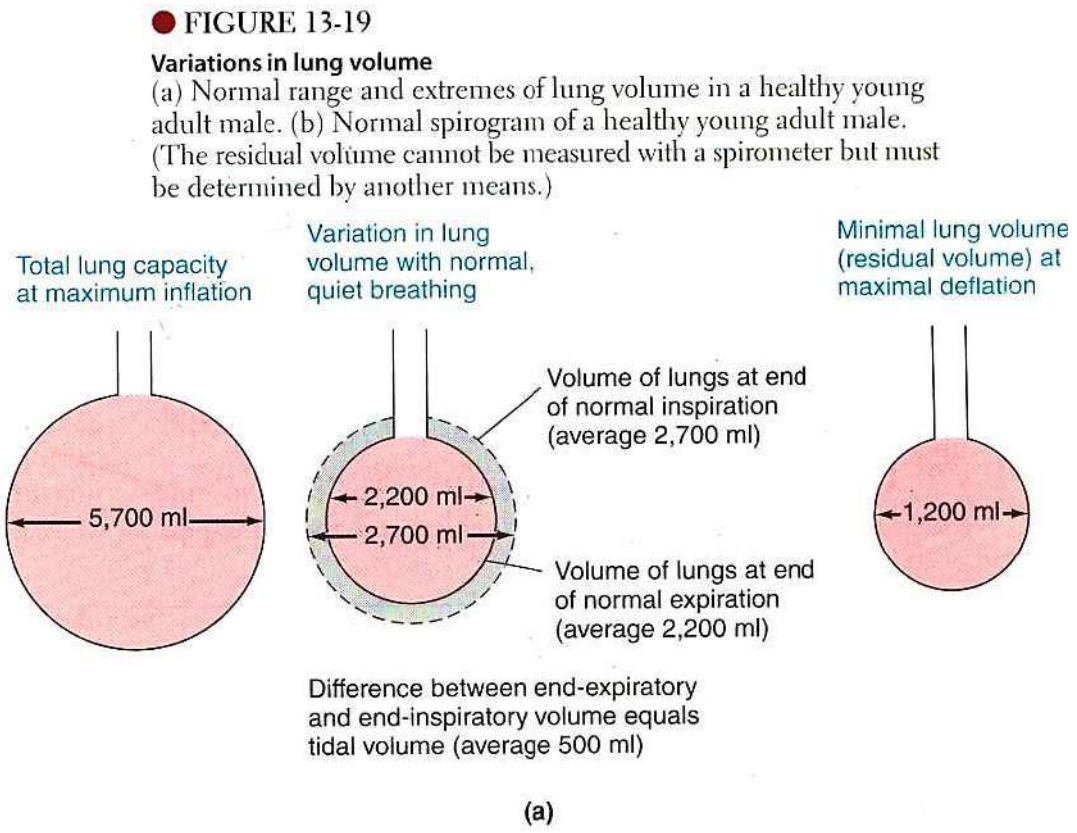
3- *When elastic recoil is decreased*, with emphysema, passive expiration may be inadequate to expel the volume of air normally exhaled during quiet breathing. Thus the abdominal muscles must work to aid in emptying the lungs, even when the person is at rest.

4- *When there is a need for increased ventilation*, such as during exercise, more work is required to accomplish both a greater depth of breathing and a faster rate of breathing.

- During strenuous exercise, the amount of energy required may increase up to 25-fold, still represents only about 5% of total energy expended. In contrast, in patients with poorly compliant lungs or obstructive lung disease, the energy required for breathing even at rest may increase to 30% of total energy expenditure, so the individual's exercise ability is severely limited, as breathing itself becomes exhausting.

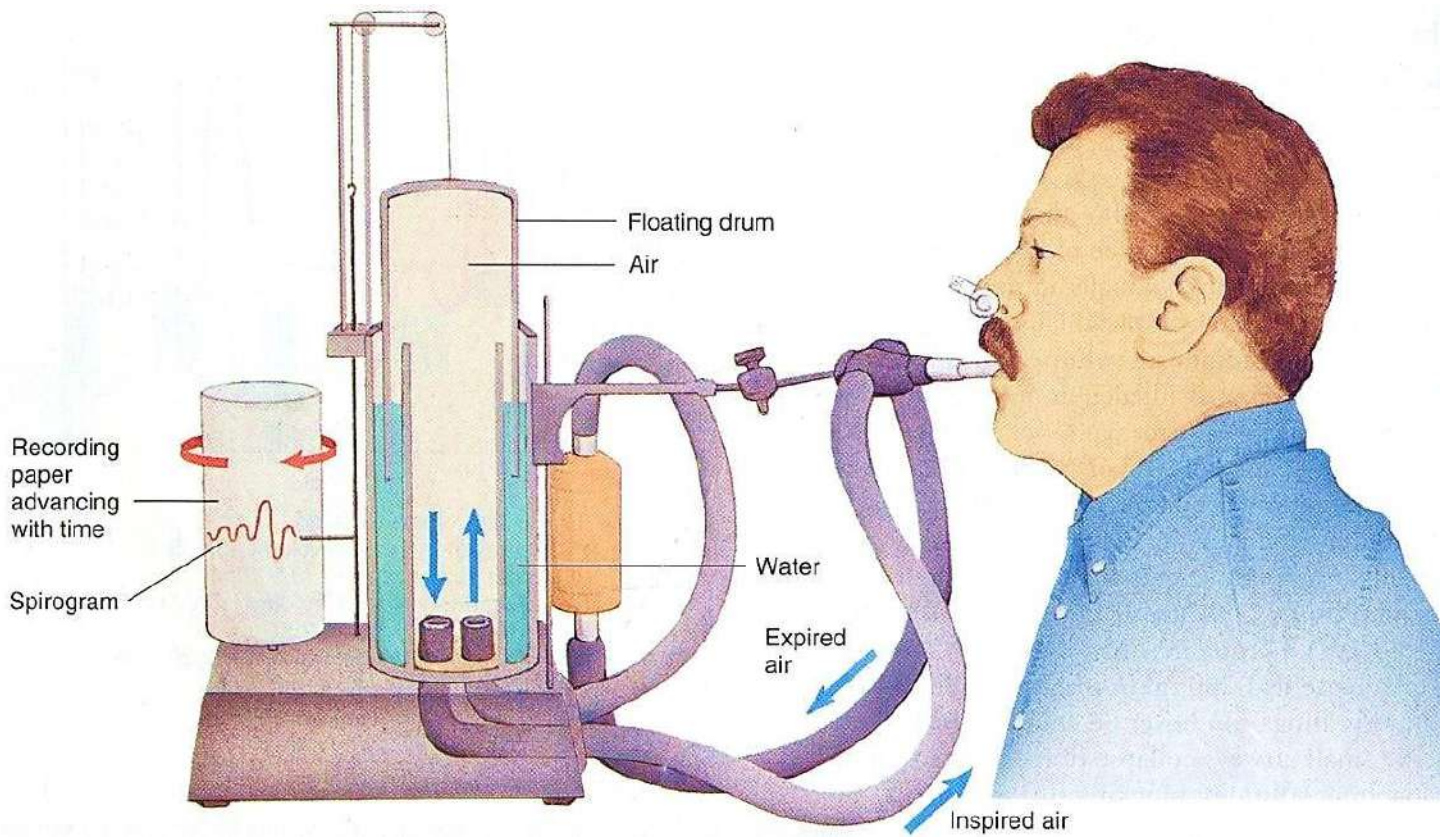
The lungs normally operate at about “half full”

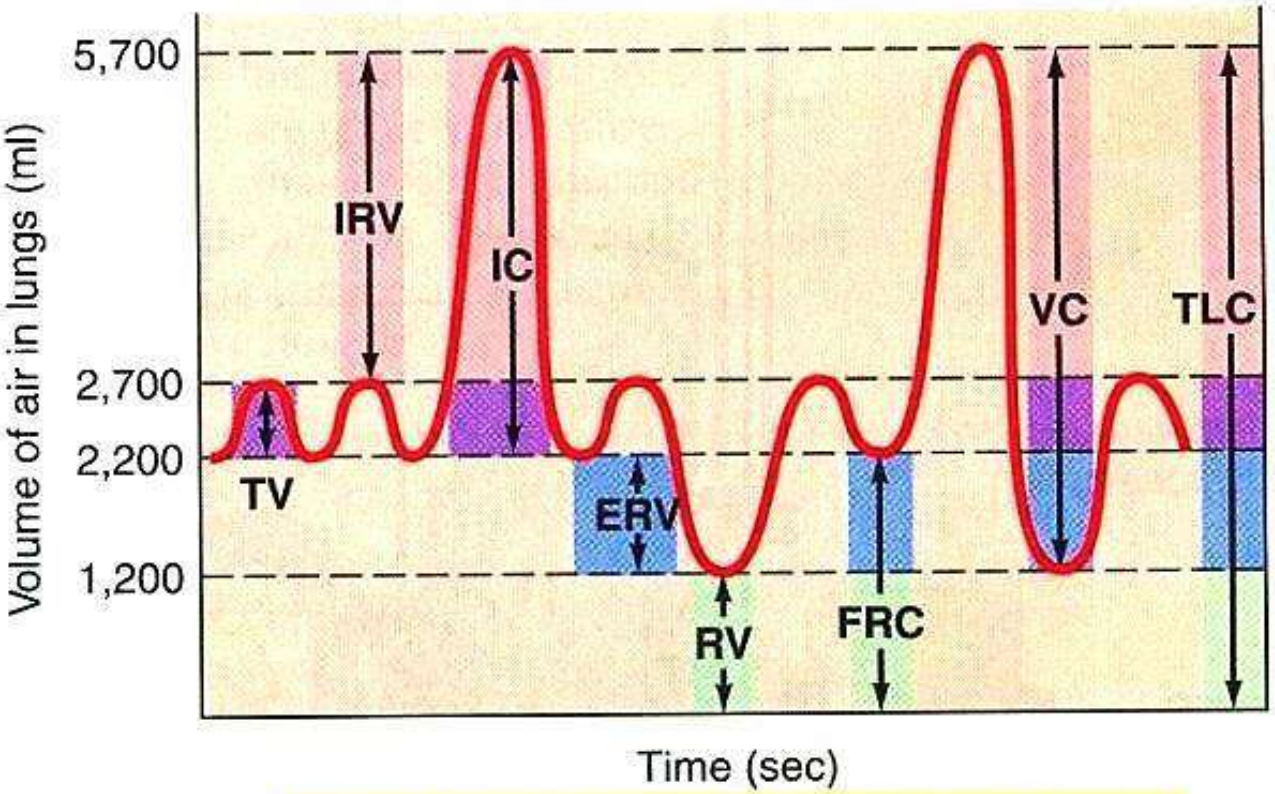
- The maximum air that the lungs can hold is about 5.7 L in males(4.2L in females). Anatomic build, age, the dispensability of the lungs, and the presence or absence of respiratory disease affect this total lung capacity.
- At the end of a normal quiet expiration, the lungs still contain about 2,200 ml of air, under resting conditions, about 500 ml of air are inspired and the same quantity is expired.
- During maximal expiration, lung volume can decrease to 1,200 ml in males (1,000 ml in females, but the lungs can never be completely deflated. Another advantage of the lungs not completely emptying with each breath is a reduction in the work of breathing . The changes in lung volume that occur with different respiratory efforts can be measured using a **spirometer**.



Lung volumes and capacities

- Basically, a **spirometer** consists of an air-filled drum floating in a water-filled chamber, the drum rises and falls in the water chamber (Fig. 13-20), can be recorded as a **spirogram**, which is calibrated to volume changes.





TV = Tidal volume (500 ml)
IRV = Inspiratory reserve volume (3,000 ml)
IC = Inspiratory capacity (3,500 ml)
ERV = Expiratory reserve volume (1,000 ml)
RV = Residual volume (1,200 ml)
FRC = Functional residual capacity (2,200 ml)
VC = Vital capacity (4,500 ml)
TLC = Total lung capacity (5,700 ml)

(b)

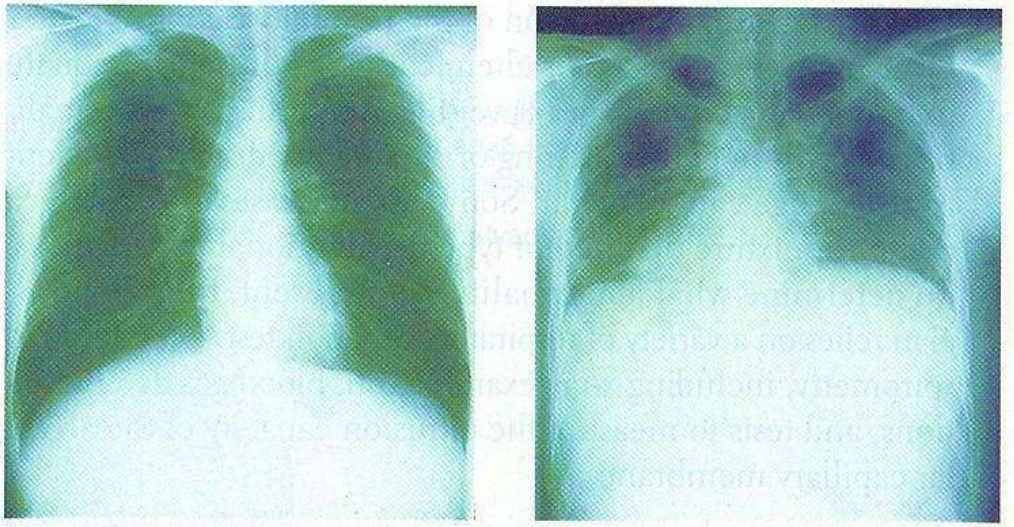
Values are average for a healthy young adult male; values for females are somewhat lower.

The following lung volumes and lung capacities (a lung capacity is the sum of two or more lung volumes) can be determined:

- **Tidal volume (TV)**, the volume of air entering or leaving the lungs during a single breath. Average value under resting conditions =500ml.
- **Inspiratory reserve volume (IRV)**, the extra volume of air that can be maximally inspired over and above the typical resting tidal volume, accomplished by maximal contraction of the diaphragm, external intercostal muscles, and accessory inspiratory muscles, (3,000ml).
- **Inspiratory capacity (IC)**, the maximum volume of air that can be inspired at the end of a normal quiet expiration **(IC=IRV + TV)**, (3,500ml).
- **Expiratory reserve volume (ERV)**, the extra volume of air that can be actively expired by maximal contraction of the expiratory muscles beyond that normally passively expired at the end of a typical resting tidal volume, (1,000ml).
- **Residual volume (RV)**, the minimum volume of air remaining in the lungs after a maximal expiration, (1,200ml), cannot be measured directly with a spirometer. It can be determined indirectly, through gas dilution techniques involving inspiration of a known quantity of a harmless tracer gas such as helium.

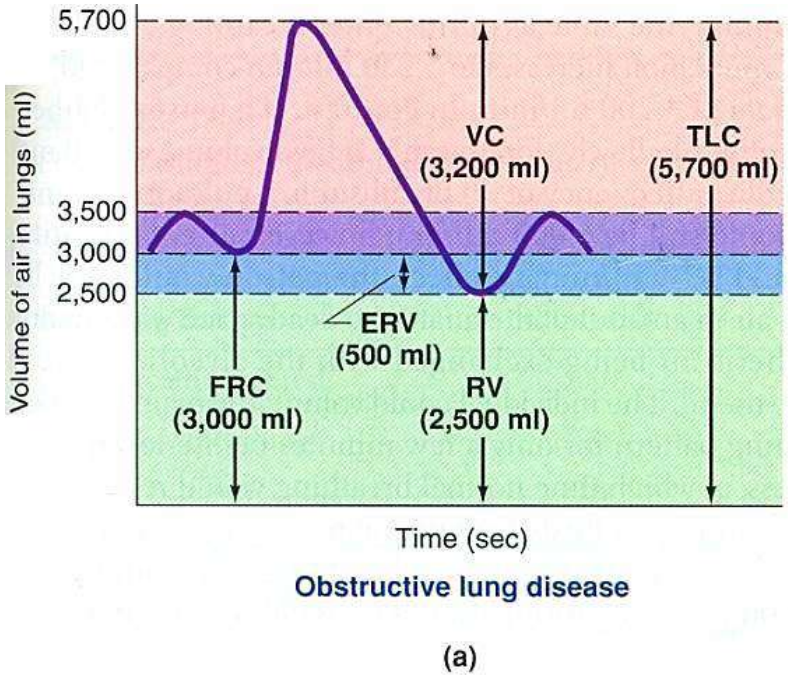
The following lung volumes and lung capacities (a lung capacity is the sum of two or more lung volumes) can be determined:

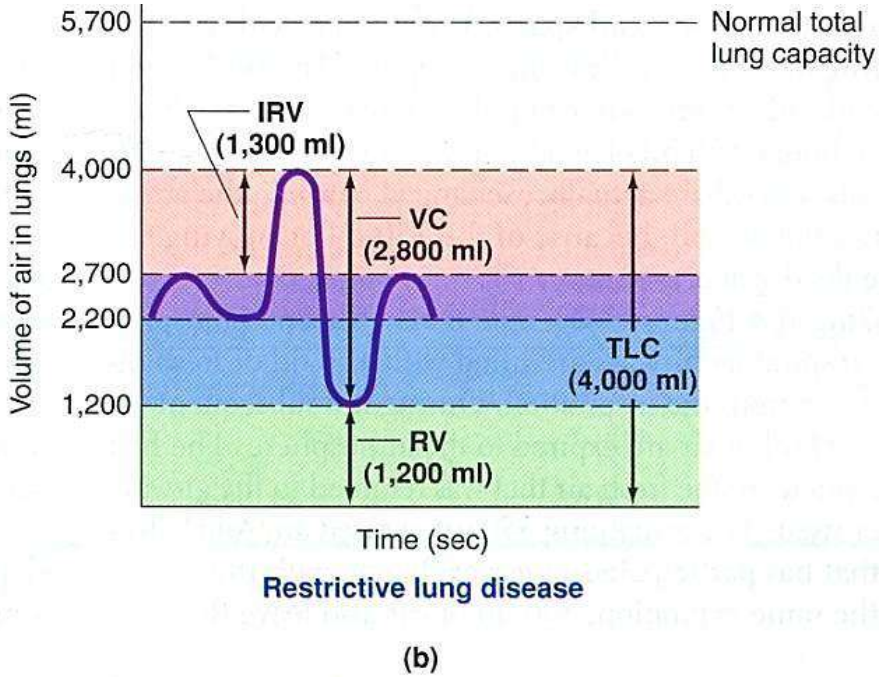
- **Functional residual capacity (FRC)**, the volume of air in the lungs at the end of a normal passive expiration **(FRC=ERV+RV)**, 2,200ml.
- **Vital capacity (VC)**, the maximum volume of air that can be moved out during a single breath following a maximal inspiration, **(VC=IRV+TV+ERV)**, it represents the maximum volume change possible within the lungs (fig. 13-21), it is useful in ascertaining the functional capacity of the lungs, (4,500ml).
- **Total lung capacity (TLC)**, the maximum volume of air that the lungs can hold, **(TLC=VC+RV)**, (5,700ml).
- **Forced expiratory volume in one second (FEV_1)**, the volume of air that can be expired during the fires second of expiration in a VC determination, usually, FEV_1 is about 80% of VC.



Respiratory dysfunction

- Such determinations are useful to the diagnostician in various respiratory disease states. Two general categories of respiratory dysfunction yield abnormal results during spirometry; ***obstructive lung disease*** and ***restrictive lung disease***.
- Other conditions affecting respiratory function include (1) diseases impairing diffusion of O_2 and CO_2 across the pulmonary membranes, (2) reduced ventilation because of mechanical failure, as with neuromuscular disorders affecting the respiratory muscles and others, (3) failure of adequate pulmonary blood flow, (4) ventilation/ perfusion abnormalities involving a poor matching of air and blood so that efficient gas exchange cannot occur.
- Some lung diseases are actually a complex mixture of different types of functional disturbances.





Alveolar ventilation is less than pulmonary ventilation because of the presence of dead space

- Various changes in lung volume represent only one factor in the determining **pulmonary ventilation**;

Pulmonary ventilation = tidal volume × respiratory rate

- At an average tidal volume of 500 ml/breath and a respiratory rate of 12 breaths/minute, pulmonary ventilation is 6,000 ml (6L), can voluntarily increase his total pulmonary ventilation 25 fold, to 150 L/min. It is usually more advantageous to have a greater increase in tidal volume than in respiratory rate, because of anatomic dead space.
- **Anatomic dead space**
- Not all the inspired air gets down to the site of gas exchange in the alveoli, because part reminds in the conducting airways, averages 150ml.
- Anatomic dead space affects efficiency of pulmonary ventilation, because only 350 ml are actually exchanged between the atmosphere and the alveoli (fig. 13-23) .

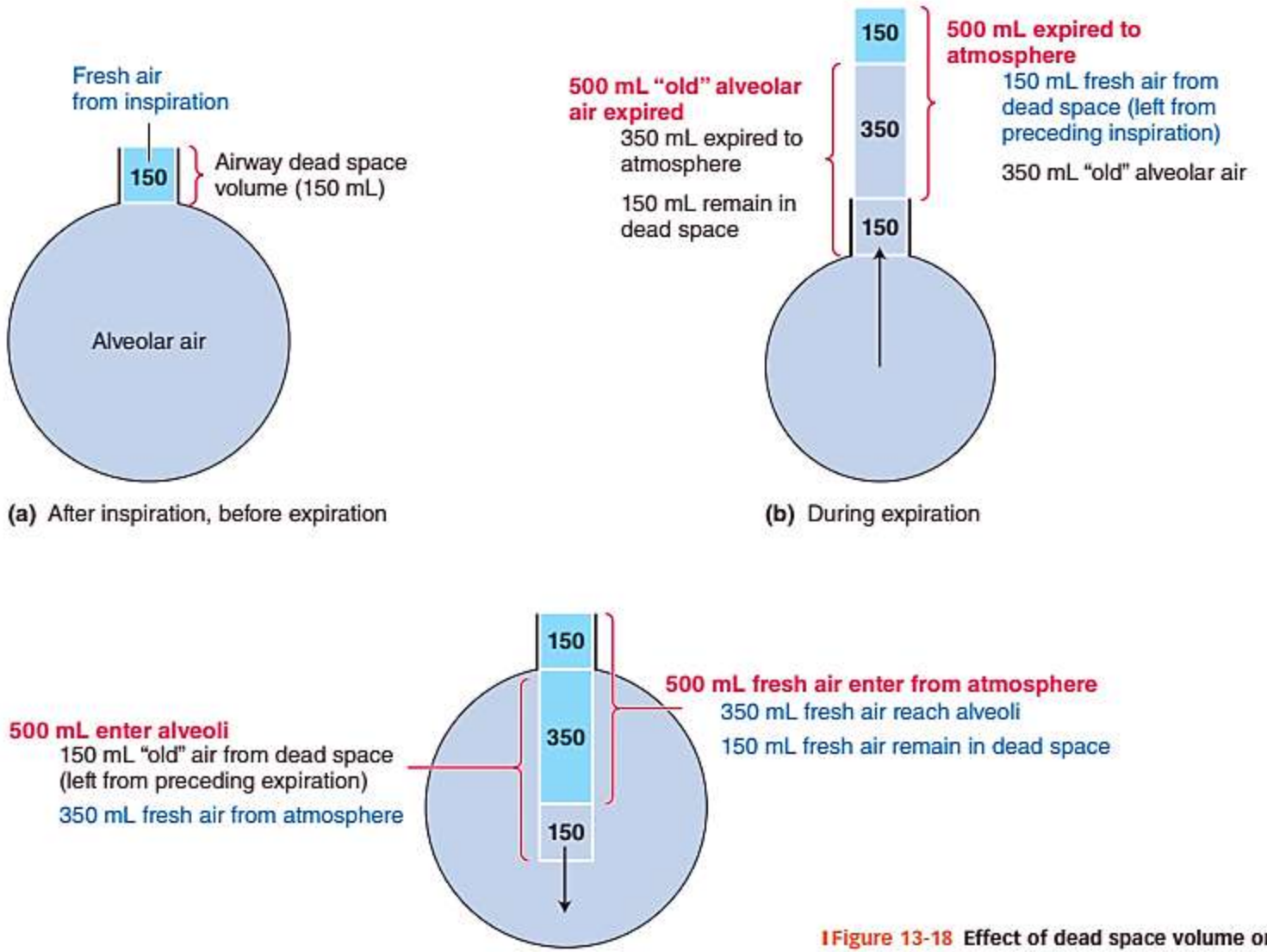


Figure 13-18 Effect of dead space volume on exchange of tidal volume between the atmosphere and the alveoli. Even though 500 mL of air move in and out between the atmosphere and the respiratory system and 500 mL move in and out of the alveoli with each breath, only 350 mL are actually exchanged between the atmosphere and the alveoli because of the anatomic dead space (the volume of air in the respiratory airways).

Alveolar ventilation

- Alveolar ventilation, the volume of air exchanged between the atmosphere and the alveoli in one minute, is a measure of the air actually available for gas exchange with the blood.
- Alveolar ventilation is more important than pulmonary ventilation:

Alveolar = (tidal volume – dead space volume) × respiratory rate

= 4,200 ml/min.

Thus with quiet breathing, alveolar ventilation is 4,200 ml/min, whereas pulmonary ventilation is 6,000 ml/min.

➢ **Effect of breathing patterns on alveolar ventilation**

To understand how important dead space volume is in determining the magnitude of alveolar ventilation, examine the effect of various breathing patterns on alveolar ventilation, as shown in (table 13-4).

TABLE 13-3 Effect of Different Breathing Patterns on Alveolar Ventilation

Breathing Pattern	Tidal Volume (mL/breath)	Respiratory Rate (breaths/min)	Dead Space Volume (mL)	Pulmonary Ventilation (mL/min)*	Alveolar Ventilation (mL/min)†
Quiet breathing at rest	500	12	150	6000	4200
Deep, slow breathing	1200	5	150	6000	5250
Shallow, rapid breathing	150	40	150	6000	0

*Equals tidal volume × respiratory rate.
†Equals (tidal volume − dead space volume) × respiratory rate.

- The individual could voluntarily maintain such a breathing pattern for only a few minutes before losing consciousness, at which time normal breathing would resume.
- The value of reflexly bringing about a larger increase in depth of breathing than in rate of breathing when pulmonary ventilation increases during exercise, should now be apparent.
- When tidal volume is increased, elevate alveolar ventilation, whereas an increase in respiratory rate does not increase alveolar ventilation, with which air is wasted in the dead space also increases.

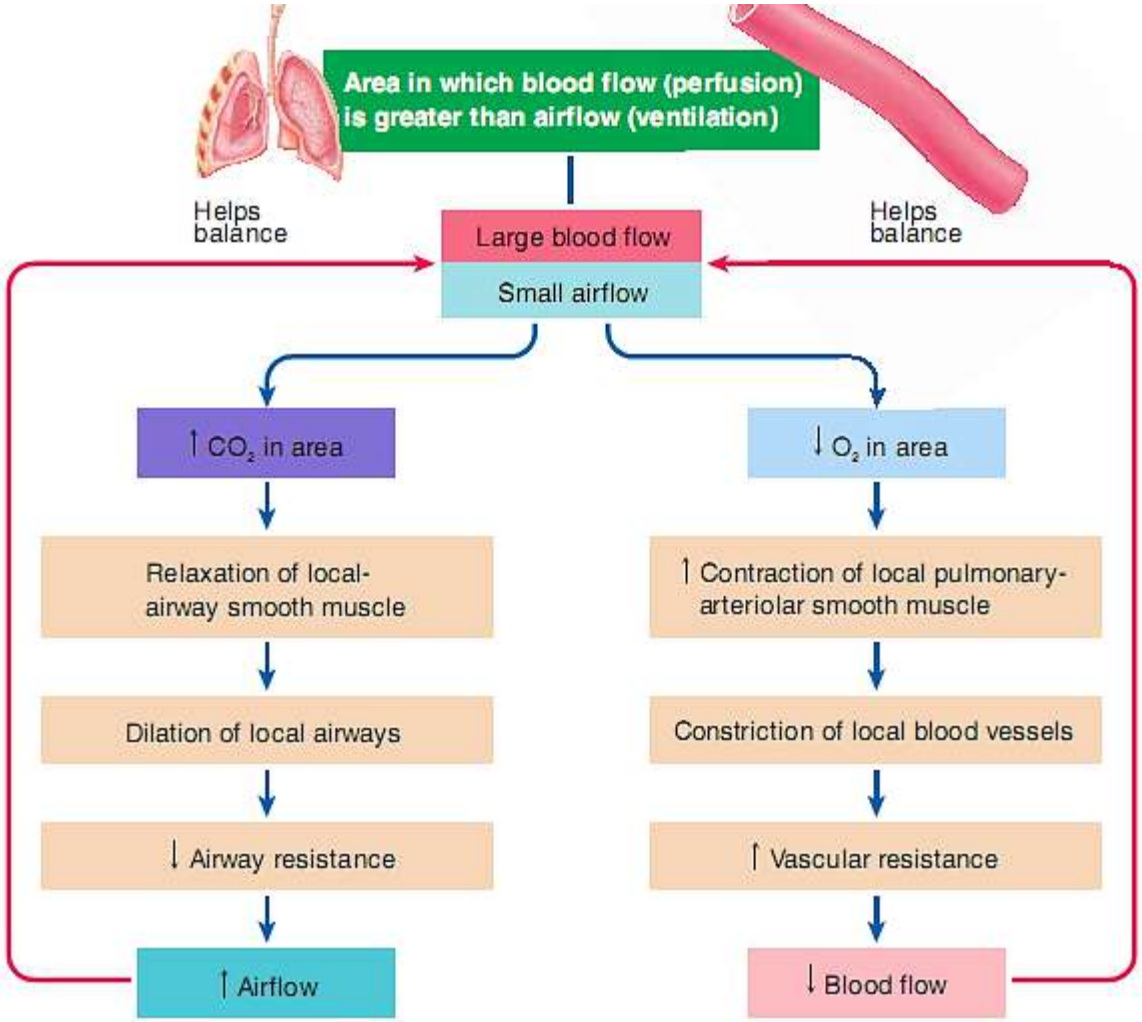
Alveolar dead space

- The match between air and blood is not always perfect, because not all alveoli are equally ventilated with air and perfused with blood. Any ventilated alveoli that do not participate in gas exchange with blood because they are inadequately perfused are considered **alveolar dead space**.

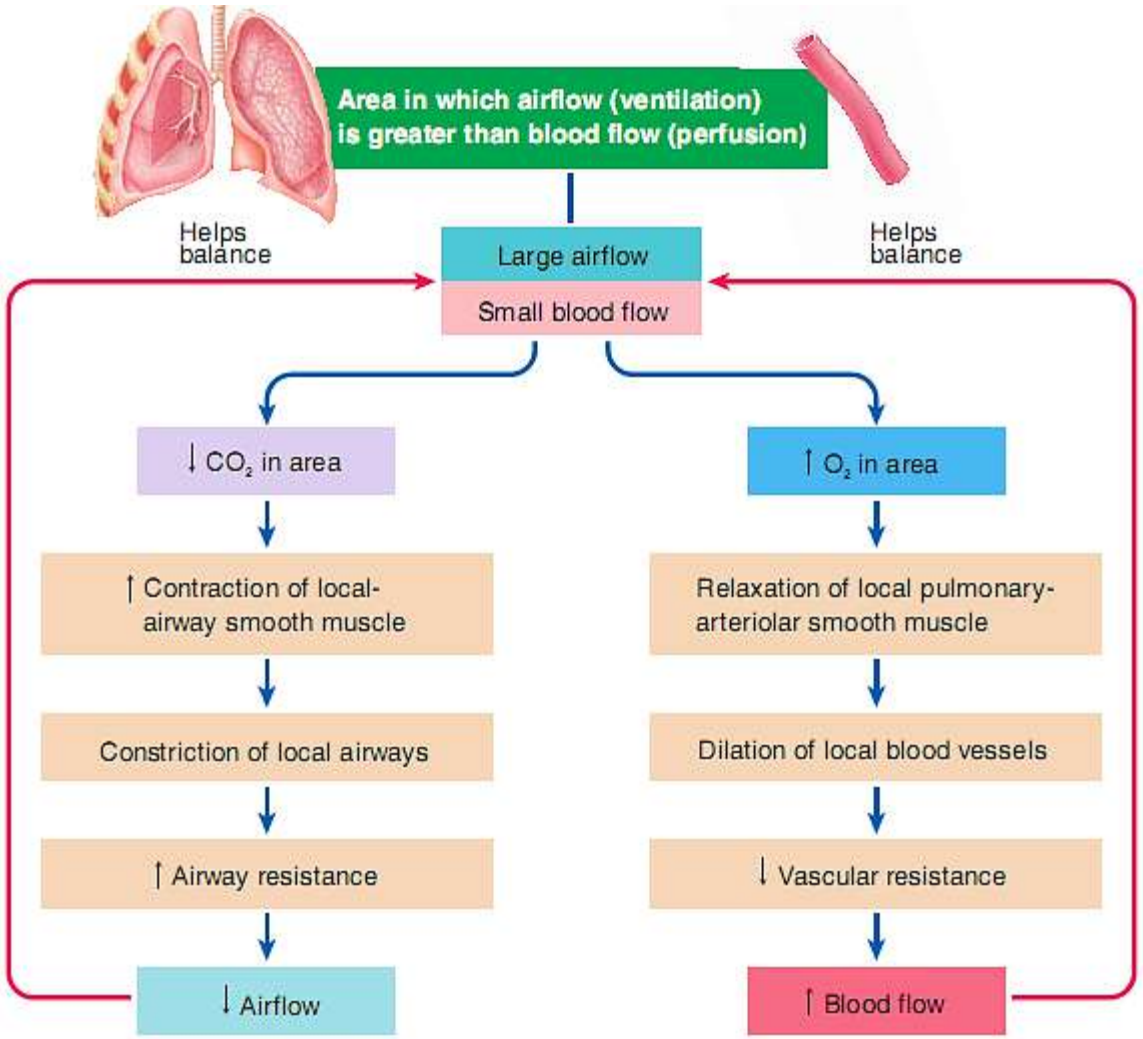
- **Local controls act on the smooth muscle of the airways and arterioles to match airflow to blood flow**
- The resistance of individual airways supplying specific alveoli can be adjusted independently in response to changes in the airway's local environment, (yet the caliber of individual arterioles supplying various tissues can be adjusted locally to match the tissues differing metabolic needs).

Effect of CO_2 on bronchiolar smooth muscle

- Bronchiolar smooth muscle is sensitive to local CO_2 levels. If an alveolus is receiving too little airflow (ventilation) in comparison to its blood flow (perfusion), CO_2 levels will increase in the alveolus, the bronchiolar smooth muscle involved to induce the airway supplying the underaerated alveolus to relax. Thus decrease in airway resistance leads to an increased airflow to the involved alveolus.
- So, its airflow now matches its blood supply (fig. 13-24), and vice versa.



(a) Local controls to adjust ventilation and perfusion to lung area with large blood flow and small airflow



(b) Local controls to adjust ventilation and perfusion to a lung area with large airflow and small blood flow

Effect of O_2 on pulmonary arteriolar smooth muscle

- Simultaneously,, a similar locally induced effect on pulmonary vascular smooth muscle also takes place, to maximally match blood flow to airflow. Just as in the systemic circulation, distribution of the cardiac output to different alveolar capillary networks can be controlled by adjusting the resistance to blood flow through specific pulmonary arterioles.
- This local effect of O_2 on pulmonary arteriolar smooth muscle is, appropriately, just the opposite of its effect on systemic arteriolar smooth muscle, (table 13-5).
- So normally very little air or blood is wasted in the lung, airflow and blood flow at a particular alveolar interface are usually matched as much as possible by these local controls to accomplish efficient exchange of O_2 and CO_2.

TABLE 13-4 Effects of Local Changes in O_2 on Pulmonary and Systemic Arterioles

	EFFECT OF A LOCAL CHANGE IN O_2	
Vessels	**Decreased O_2**	**Increased O_2**
Pulmonary arterioles	Vasoconstriction	Vasodilation
Systemic arterioles	Vasodilation	Vasoconstriction

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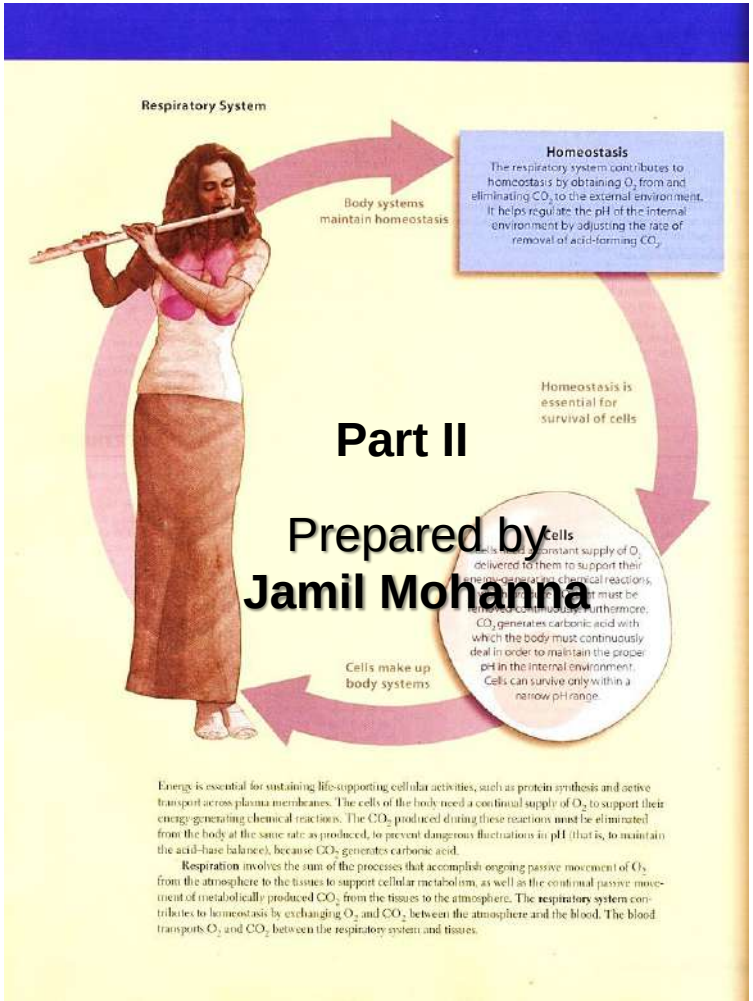
Chapter 13

The Respiratory System



Energy is essential for sustaining life-supporting cellular activities, such as protein synthesis and active transport across plasma membranes. The cells of the body need a continual supply of O_2 to support their energy-generating chemical reactions. The CO_2 produced during these reactions must be eliminated from the body at the same rate as produced, to prevent dangerous fluctuations in pH (that is, to maintain the acid–base balance), because CO_2 generates carbonic acid.

Respiration involves the sum of the processes that accomplish ongoing passive movement of O_2 from the atmosphere to the tissues to support cellular metabolism, as well as the continual passive movement of metabolically produced CO_2 from the tissues to the atmosphere. The **respiratory system** contributes to homeostasis by exchanging O_2 and CO_2 between the atmosphere and the blood. The blood transports O_2 and CO_2 between the respiratory system and tissues.

Part II

Prepared by

Jamil Mohanna

Gas exchange

Gases move down partial pressure gradients

- O_2 and CO_2 move across body membranes by passive diffusion down partial pressure gradients. No active transport mechanisms exist for these gases.

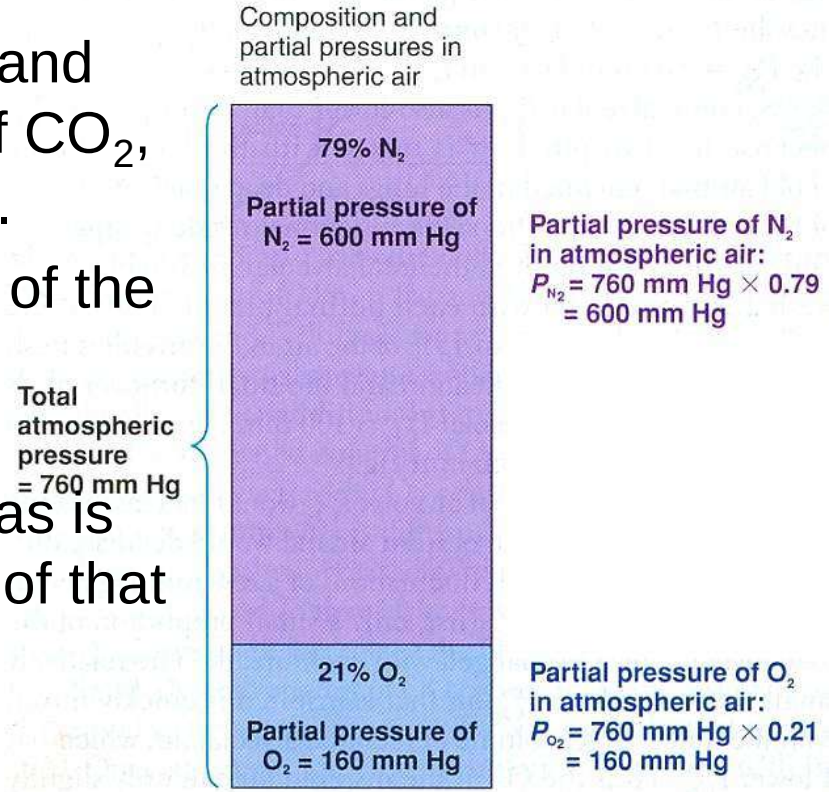
Partial pressures

- Typical dry air contains about 79% N_2 and 21% O_2, with negligible percentages of CO_2, H_2O vapor, other gases and pollutants.
- This total pressure is equal to the sum of the pressures that each gas in the mixture partially contributes.
- The pressure exerted by a particular gas is directly proportional to the percentage of that gas in the total air mixture (fig.13-25).

FIGURE 13-25

Concept of partial pressures

The partial pressure exerted by each gas in a mixture equals the total pressure times the fractional composition of the gas in the mixture.



- The individual pressure exerted independently by a particular gas within a mixture of gases is **partial pressure (P_{gas})**, thus Po_2 =160 mm Hg and Pco_2 = is negligible = 0.03 mm Hg.

  Gases dissolved in a liquids; the greater the partial pressure of a gas, the more of that gas dissolved.

- **Partial pressure gradients**, is a difference in partial pressure between capillary blood and surrounding structures, e.g. the alveolar air and surrounding tissues. A gas always diffuses down its partial pressure gradient from the area of higher partial pressure to the area of lower partial pressure, similar to diffusion down a concentration gradient.

O_2 enters and CO_2 leaves the blood in the lungs *passively* down partial pressure gradients

Alveolar Po_2 and PCO_2

- Alveolar air is not of the same composition as inspired atmospheric air, for two reasons; ***first***, humidification of inspired air in effect "dilutes" the partial pressure of the inspired gases by 47 mm Hg, PN_2= 563 mm Hg, and Po_2= 150 mm Hg; ***second***, alveolar Po_2 is also lower than atmospheric Po_2 because fresh inspired air is mixed with the large volume of old air that remained in the lungs and dead space at the end of the preceding expiration.
- Only about 1/7 of the total alveolar air is replaced by fresh atmospheric air (15% of the air in the alveoli is fresh air). As a result of humidification and the small turnover of alveolar air, the average alveolar Po_2 is 100 mm Hg.
- During inspiration , only small fluctuations of a few mm Hg occur, for two reasons; (1) only a small proportion of the total alveolar air is exchanged with each breath. (2) Oxygen is continually moving by passive diffusion.
- Therefore, the alveolar Po_2 remains relatively constant at about 100 mm Hg throughout the respiratory cycle.
- Because the pulmonary blood Po_2 equilibrates with the alveolar Po_2, the Po_2 of the blood leaving the lungs remains fairly constant at this same value.
- A similar situation exists in reverse for CO_2 (fig. 13-26) Animation .

O_2 enters and CO_2 leaves the blood in the lungs passively down partial pressure gradients

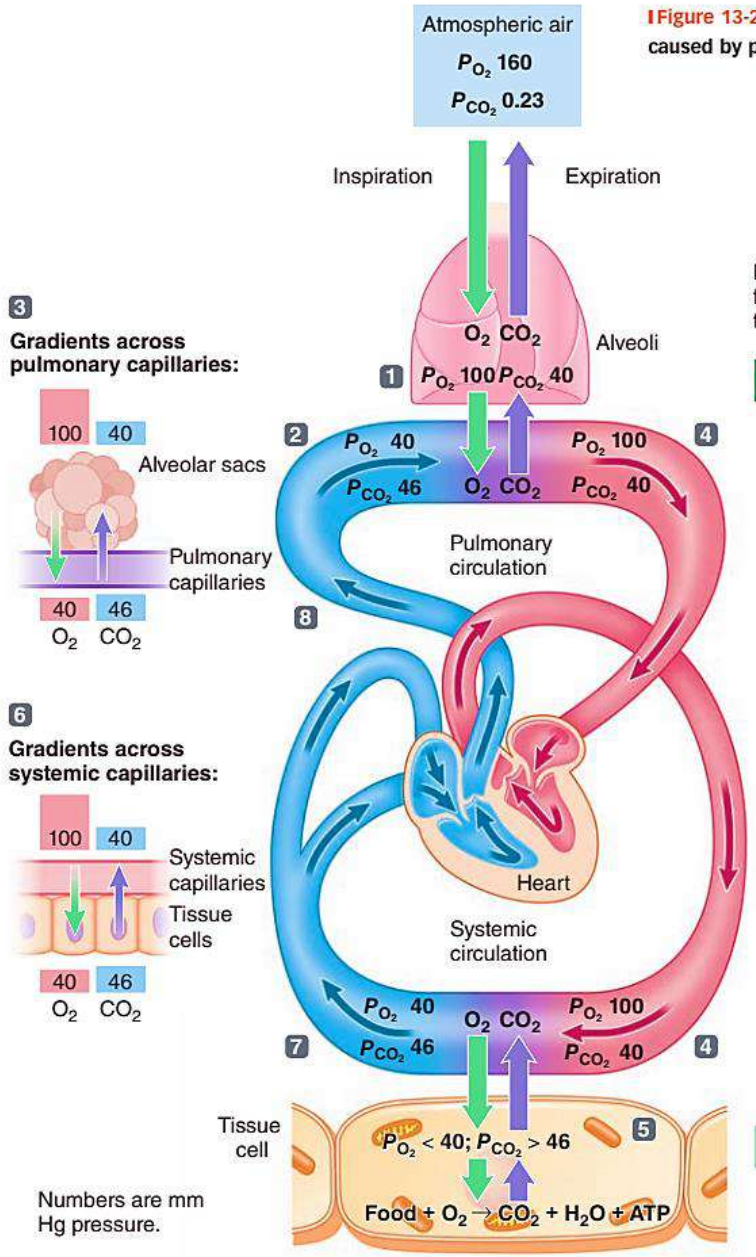


Figure 13-22 O_2 and CO_2 exchange across pulmonary and systemic capillaries caused by partial pressure gradients.

1. Alveolar P_{O_2} remains relatively high and alveolar P_{CO_2} remains relatively low because a portion of the alveolar air is exchanged for fresh atmospheric air with each breath.
2. In contrast, the systemic venous blood entering the lungs is relatively low in O_2 and high in CO_2, having given up O_2 and picked up CO_2 at the systemic capillary level.
3. The partial pressure gradients established between the alveolar air and pulmonary capillary blood induce passive diffusion of O_2 into the blood and CO_2 out of the blood until the blood and alveolar partial pressures become equal.
4. The blood leaving the lungs is thus relatively high in O_2 and low in CO_2. It arrives at the tissues with the same blood-gas content as when it left the lungs.
5. The partial pressure of O_2 is relatively low and that of CO_2 is relatively high in the O_2-consuming, CO_2-producing tissue cells.
6. Consequently, partial pressure gradients for gas exchange at the tissue level favor the passive movement of O_2 out of the blood into cells to support their metabolic requirements and also favor the simultaneous transfer of CO_2 into the blood.
7. Having equilibrated with the tissue cells, the blood leaving the tissues is relatively low in O_2 and high in CO_2.
8. The blood then returns to the lungs to once again fill up on O_2 and dump off CO_2.

- Note that the blood returning to the lungs from the tissues still contains O_2 and that blood leaving the lungs still contain CO_2 represents an immediately available O_2 reserve that can be tapped by the tissue cells whenever their O_2 demands increase. The CO_2 remaining, plays an important role in the acid-base balance of the body, because CO_2 generates carbonic acid and it is important in driving respiration as we will see.

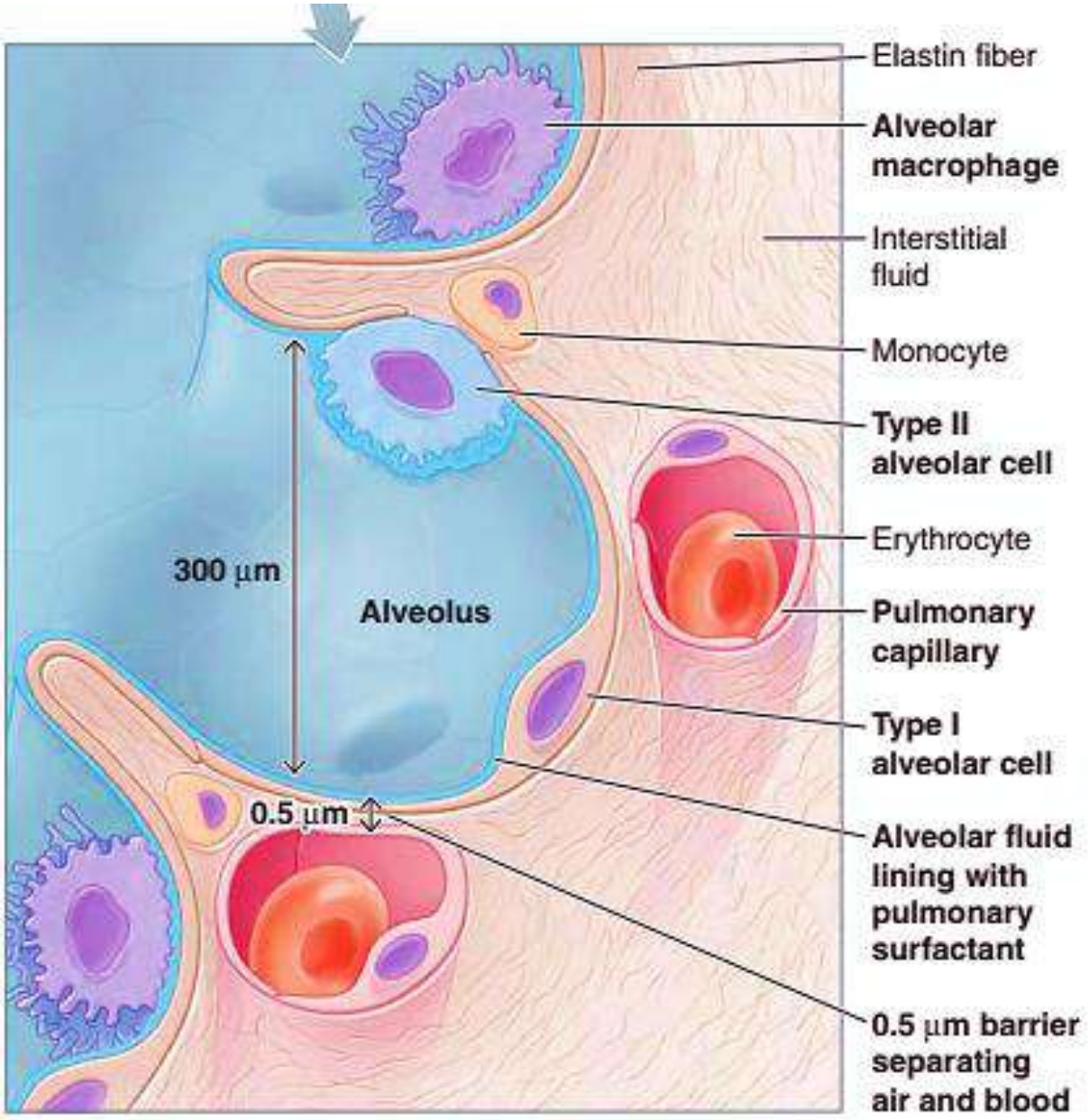
- When the tissues metabolize more actively, they extract more O_2 from the blood, reducing the systemic venous Po_2 to 30 mm Hg (step ❼), a large Po_2 gradient exists. The difference in Po2 between the alveoli and blood is now 70 mm Hg, more O_2 diffuses from the alveoli into the blood down the larger partial pressure gradient before blood Po_2 equals alveolar Po_2.
- Replaces the increased amount of O_2 consumed, so O_2 uptake matches O_2 use even when O_2 use even when O_2 consumption increases, ventilation is stimulated so that O_2 enters the alveoli more rapidly from the atmosphere to replace the O_2 diffusing into the blood.
- Similarly, an increased ventilation associated with increased activity ensures that increased CO_2 delivered to the alveoli is blown off to the atmosphere.

Factors other than the partial pressure gradient influence the rate of gas transfer

- According to Fick's law of diffusion, rate of a gas through a sheet of tissue also depends on the surface area and thickness of the membrane through which the gas is diffusing and on the diffusion coefficient of the particular gas (table 13-5).

TABLE 13-5 Factors That Influence the Rate of Gas Transfer Across the Alveolar–Capillary Membrane

Factor	Influence on the Rate of Gas Transfer Between Air and Blood	Comments
Partial pressure gradients of O_2 and CO_2	Rate of transfer ↑ as partial pressure gradient ↑	Major determinant of the rate of transfer
Surface area of the alveolar–capillary membrane	Rate of transfer ↑ as surface area ↑	Surface area remains constant under resting conditions Surface area ↑ during exercise Surface area ↓ with pathological conditions such as emphysema and lung collapse
Thickness of the alveolar–capillary membrane	Rate of transfer ↓ as thickness ↑	Thickness normally remains constant Thickness ↑ with pathological conditions such as pulmonary edema, pulmonary fibrosis, and pneumonia
Diffusion constant	Rate of transfer ↑ as diffusion constant ↑	Diffusion constant for CO_2 is 20 times that of O_2, offsetting the smaller partial pressure gradient for CO_2; therefore, approximately equal amounts of CO_2 and O_2 are transferred across the membrane



(a) Alveolus and surrounding pulmonary capillaries

Effect of surface area on gas exchange

- During resting conditions, some of the pulmonary capillaries are typically closed, because the normally low pressure. During exercise, when the pulmonary blood pressure is raised they are forced to open, increases the surface area of blood available for exchange. Furthermore, the alveolar membranes are stretched further than normal during exercise because of the larger tidal volumes (deeper breathing), increases the alveolar surface area and decreases the thickness of the alveolar membrane.
- Reduction in the surface area may happens; in emphysema because many alveolar walls are lost, resulting in larger but fewer chambers (fig. 13-27), and associated with collapsed regions of the lung and also results when part of the lung tissue is surgically removed in treating lung cancer.

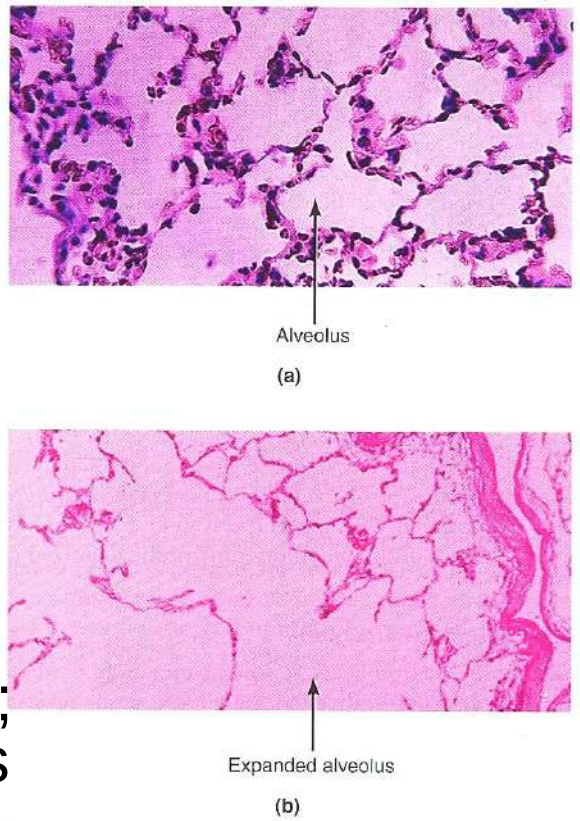


FIGURE 13-27
Comparison of normal and emphysematous lung tissue
(a) Photomicrograph of lung tissue from a normal individual. Each of the smallest clear spaces is an alveolar lumen. (b) Photomicrograph of lung tissue from a patient with emphysema. Note the loss of alveolar walls in the emphysematous lung tissue, resulting in larger but fewer alveolar chambers.

Effect of thickness on gas exchange

- The rate of gas transfer decreases, because a gas takes longer to diffuse through the greater thickness, in

(1) ***Pulmonary edema***, an excess accumulation of interstitial fluid between the alveoli and pulmonary capillaries caused by pulmonary inflammation or left-sided congestive heart failure;

(2) ***Pulmonary fibrosis***, involving replacement of delicate lung tissue with thick fibrous tissue in response to certain chronic irritants;

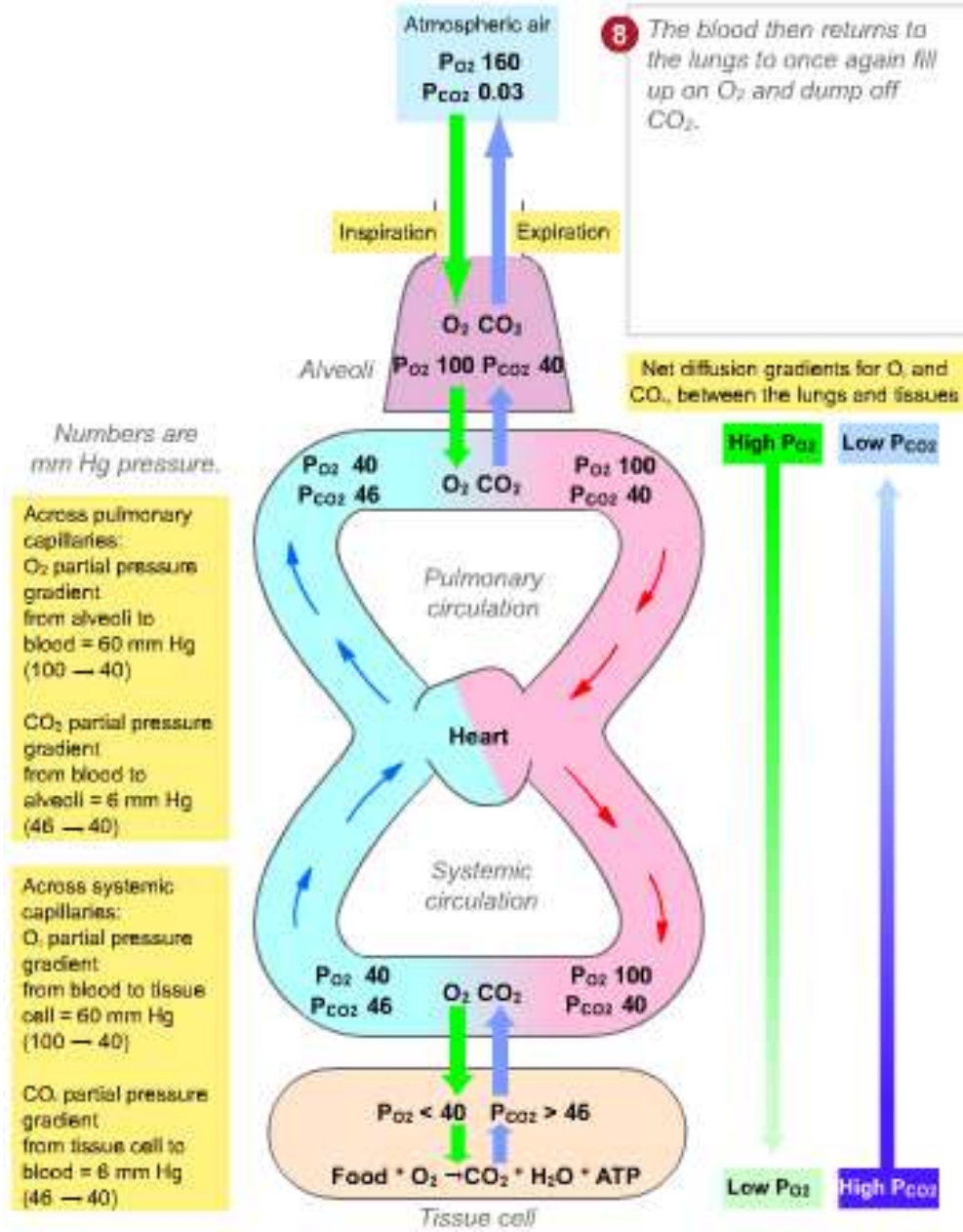
(3) ***Pneumonia***, which characterized by inflammatory fluid accumulation within or around the alveoli, due to bacterial or viral infection of the lungs, also arise from accidental *aspiration* of food, vomitus, or chemical agents.

Effect of the diffusion coefficient on gas exchange

- the rate of gas transfer is directly proportional to **the diffusion coefficient (D)**, a constant value related to the solubility of a particular gas in the lung tissues and to its molecular weight **(D α sol √mw)**, is normally offset by the difference in partial pressure gradients.
- Normally, approximately equal amounts of O_2 and CO_2 are exchanged – a respiratory quotient's worth. Even though a given volume of blood spends three-fourths of a second passing through the pulmonary capillary bed, Po_2 and CO_2 are usually both equilibrated with alveolar partial pressures by the time the blood has traversed only 1/3 the length of the pulmonary capillaries. This means that the lung normally has enormous diffusion reserves, a fact that becomes extremely important during heavy exercise. even when less time is available for exchange.
- In a diseased lung in which diffusion is impeded because the surface area is decreased or the blood – air barrier is thickened, O_2 transfer is usually more seriously impaired than CO_2 transfer, because of the larger CO_2 diffusion coefficient.

Net diffusion of O_2 and CO_2 between the alveoli and tissues

- Net diffusion of O_2 occurs because of the O_2 partial pressure gradients created by continuous replenishment of fresh alveolar O_2 provided by alveolar ventilation.
- Net diffusion of CO_2 occurs in the reverse direction, because of the CO_2 partial pressure gradients created by continuous production of CO_2 in the cells and the continuous removal of alveolar CO_2 through the process of alveolar ventilation (fig. 13-26).



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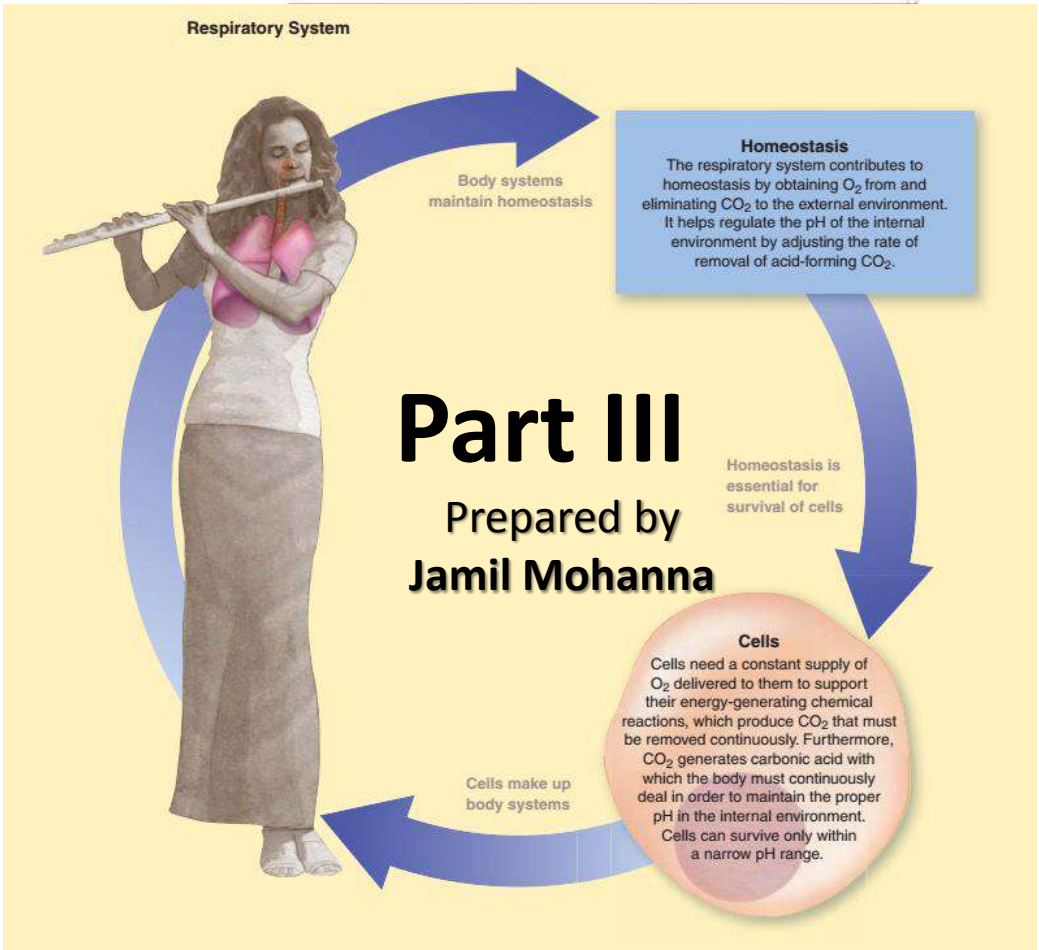
Chapter 13

The Respiratory System



Part III

Prepared by

Jamil Mohanna

Gas transport

Most O_2 in the blood is transported bound to hemoglobin

- Because O_2 and CO_2 are not very soluble in the blood, they must be transported primarily by mechanisms other than simply being physically dissolved.
- Oxygen is present in the blood in two forms: physically dissolved and chemically bound to hemoglobin (table 13-7).

$$Hb + O_2 \rightleftharpoons HbO_2$$

reduced hemoglobin oxyhemoglobin

▲ TABLE 13-6 Methods of Gas Transport in the Blood

Gas	Method of Transport in Blood	Percentage Carried in This Form
O_2	Physically dissolved	1.5
	Bound to hemoglobin	98.5
CO_2	Physically dissolved	10
	Bound to hemoglobin	30
	As bicarbonate (HCO_3^-)	60

➢ Physically dissolved O_2

- At a normal arterial Po_2 of 100 mm Hg, only 3 ml of O_2 can dissolve in 1 liter of blood, thus only 15 ml of O_2/ min. the cells consume 250 ml of O_2/min, and may increase up to 25-fold during strenuous exercise.
- Only 1.5% of the O_2 in the blood is dissolved; the remaining 98.5% is transported in combination with Hb.

➢ Oxygen bound to hemoglobin

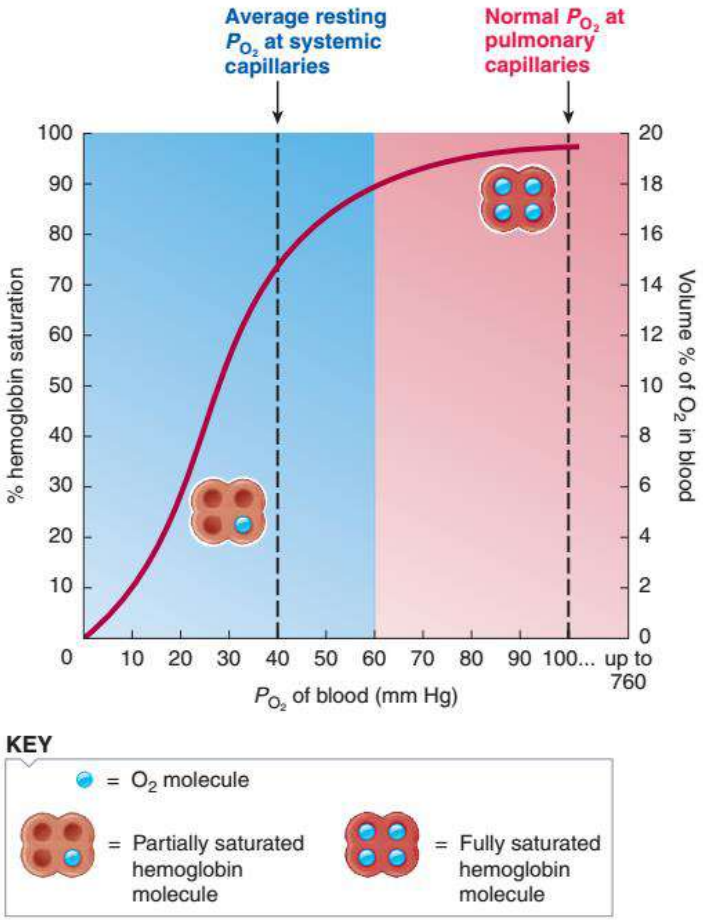
- Hemoglobin, an iron-bearing protein molecule contained within the red blood cells, can easily reversible combination with O_2:

$$\underset{\text{Reduced hemoglobin}}{Hb} + O_2 \leftrightarrows \underset{\text{oxyhemoglobin}}{HbO_2}$$

- What determines whether O_2 and Hb are combined or dissociated? Why does Hb combine with O_2 in the lungs and release O_2 at the tissues? How can a variable amount of O_2 be released at the tissues, depending on the level of tissue activity? How can we talk about O_2 transfer between blood and surrounding tissues in terms of O_2 partial pressure gradients when 98.5% of the O_2 is bound to Hb and thus does not contribute to the Po_2 of the blood at all?

The Po_2 is the primary factor determining the percent hemoglobin saturation

- Each *fully saturated* Hb molecule can carry up to four molecules of O_2. The **percent hemoglobin (%Hb) saturation**, a measure of the extent to which the Hb present is combined with O_2, can vary from 0% to 100%.
- According to the **law of mass action**, if the concentration of one substance involved in a reversible reaction is increased, the reaction is driven toward the opposite side and vice versa.
- When the blood Po_2 increases, as in the pulmonary capillaries, the reaction is driven toward the right side of the equation, increasing formation of HbO_2 (increased % Hb saturation and vice versa.
- Thus because of the difference in Po_2 at the lungs and other tissues, Hb automatically "loads up" on O_2 in the lungs, where ventilation is continually, it follows an **S**-shaped curve, the **O_2-Hb dissociation** (or **saturation**) **curve** (fig. 13-28). **Animation**



● **FIGURE 13-28 Oxygen–hemoglobin (O_2–Hb) dissociation (saturation) curve.** The % hemoglobin saturation (the scale on the left side of the graph) depends on the P_{O_2} of the blood. The relationship between these two variables is depicted by an S-shaped curve with a plateau region between a blood P_{O_2} of 60 and 100 mm Hg and a steep portion between 0 and 60 mm Hg. Another way of expressing the effect of blood P_{O_2} on the amount

- Within the curve flattens off, or plateaus, arise in PO_2 produces only a small increase in the extent to which Hb is bound with O_2. in the Po_2 range of 0 to 60 mm Hg, in contrast, a small change in PO_2 results in a large change in the extent to which Hb is combined with O_2.
- **Significance of the plateau portion of the O_2-Hb curve**
- The plateau portion exists at the pulmonary capillaries where O_2 is being loaded onto Hb, note that at a blood PO_2 of 100 mm Hg, Hb is 97.5% saturated. So, if the alveolar PO_2 and consequently the arterial PO_2 fall below normal, there is little reduction in the total amount of O_2 transported by the blood until the PO_2 falls below 60 mm Hg, because of the plateau region of the curve.
- At a blood Po_2 of 60 mm Hg, the % Hb saturation is still high at 90%, and the total O_2 content of the blood is only slightly decreased despite the 40% reduction if Po_2.
- However, even if the blood Po_2 is greatly increased- say, to 600 mm Hg by breathing pure O_2, very little additional O_2 is added to the blood.
- A small extra amount of O_2 dissolves, but the % Hb saturation can be increased by only another 2.5%. Thus the plateau portion of the O_2-Hb curve provides a good margin of safety in O_2-carryin capacity of the blood.
- Arterial Po_2 may be reduced by pulmonary diseases. It may also fall in healthy individuals under two circumstances: **(1)** at high altitude **(2)** in O_2-deprived environments at sea level.

Significance of the steep portion of the O_2-Hb curve

- The steep portion exists at the systemic capillaries, where O_2 is unloaded from Hb. The blood equilibrates with the surrounding tissue cells at an average Po_2 of 40 mm Hg (fig. 13-28), the %Hg saturation is 75%.
- Because Hb can only be 75% saturated at the Po_2 of 40 mm Hg in the systemic capillaries, nearly 25% of the HbO_2 must dissociate, this released O_2 is free to diffuse down its partial pressure gradient.
- If the tissue cells are metabolizing more actively, the Po_2 drop of 20 mm Hg in Po_2 decreases the % Hb saturation from 75% to 30%; that is about 45% more of the total HbO_2 than normal gives up its O_2 for tissue use.
- Only a small drop in systemic capillary Po_2 can automatically make large amounts of O_2 immediately available to meet the O_2 needs of more actively metabolizing tissues.
- In addition to this more withdrawal of O_2 from the blood, even more O_2 is made available, by circulatory and respiratory adjustments that increase the flow rate of oxygenated blood through the active tissues.

Hemoglobin promotes the net transfer of O_2 at both the alveolar and tissue levels

- Hb dose play a crucial role in permitting the transmitting the transfer of large quantities of O_2 before blood Po_2 equilibrates with the surrounding tissues ***(fig. 13-29)***.

Role of hemoglobin at the alveolar level

- When systemic venous blood enters the pulmonary capillaries, its Po_2 is considerably lower than the alveolar Po_2, so O_2 immediately diffuses into the blood, raising blood Po_2, the percentage of Hb that can bind with O_2 increases. Although the total quantity of O_2 in the blood actually has increased.
- Net diffusion of O_2 from alveoli to blood occurs continuously until Hb becomes as completely saturated at 100 mm Hg, Hb is 97.5 % saturated.
- Only now does the blood Po_2 rapidly equilibrate with the alveolar Po_2.

Role of hemoglobin at the tissue level

- The reverse situation occurs at the tissue level. The Po_2 of blood in the systemic capillaries is considerably higher than the Po_2 of the tissue, O_2 immediately diffuses into the tissues, lowering blood Po_2.
- Hb must unload some stored O_2, the % Hb saturation is reduced.
- Although the total quantity of O_2 in the blood has already fallen. Only when Hb can no longer release any more O_2 into solution, can blood Po_2 fall as low as in surrounding tissue.
- If Hb levels fall to one-half of normal, as in a severely anemic patient, the O_2-carrying capacity of the blood falls by 50% even though the arterial Po_2 is the normal.

Factors at the tissue level promote the unloading of O_2 from hemoglobin

- Other factors can affect the affinity, between Hb and O_2 and can shift the O_2-Hb curve at a given Po_2, CO_2, acidity, temperature, and 2,3-bisphosphoglycerate.
- All these factors shifts the O_2-Hb curve to the right (fig. 13-30), decreases the affinity of Hb for O_2. So, Hb unloads even more O2 at the tissue level.
- In actively metabolizing cells, such as exercising muscles, lactic acid also may be produced, resultant local elevation of acid , facilitates further unloading of O_2.
- The influence of CO_2 and acid on the release of O_2 is known as the **Bohr effect**.
- Indeed, the %Hb saturation decreases when CO_2 and H^+ bind with Hb, because their presence on Hb facilitates increased release of O_2 from Hb.

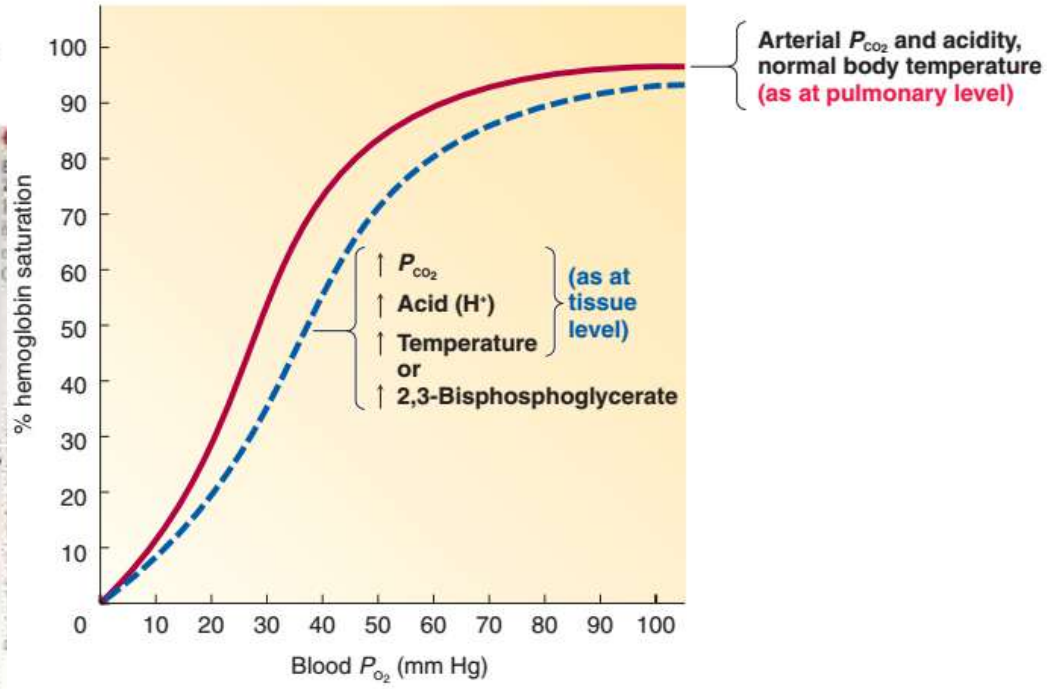


FIGURE 13-30 Effect of increased P_{CO_2}, H^+, temperature, and 2,3-bisphosphoglycerate on the O_2–Hb curve. Increased P_{O_2}, acid, and temperature, as found at the tissue level, shift the O_2–Hb curve to the right. As a result, less O_2 and Hb can be combined at a given P_{O_2} so that more O_2 is unloaded from Hb for use by the tissues. Similarly, 2,3-bisphosphoglycerate, whose production is increased in red blood cells when arterial HbO_2 is chronically below normal, shifts the O_2–Hb curve to the right, making more of the limited O_2 available at the tissue level.

Comparison of these factors at the tissue and pulmonary levels

- Increases in CO_2, acidity, and temperature at the tissue level, enhance the effect of a drop in Po_2 in facilitating the release of O_2 from Hb. Theses effects are largely reversed at the pulmonary level, where the extra acid-forming CO_2 is blown off and the local environment is cooler, enhancing the effect of raised Po_2 in loading O_2 onto Hb.
- **Effect of 2,3-bisphosphoglycerate (BPG) on % Hb saturation**
- A factor *inside* the red blood cells, produced during red blood cell metabolism, can bind reversibly with Hb and reduce its affinity for O_2, just as CO_2 and H^+ do, shifts the O_2-Hb curve to the right, enhancing O_2 unloading as the blood flows through the tissues.
- BPG production by gradually increases in the arterial blood is chronically undersaturated, arterial HbO_2 is below normal, may occur in people living at high altitudes or in those certain types of circulatory or respiratory diseases or anemia.
- Shifts the curve to the right to the same degree in both the tissues and the lungs. As a result, BPG decreases the ability to load O_2 at the pulmonary level, which is the negative side of increased BPG production.

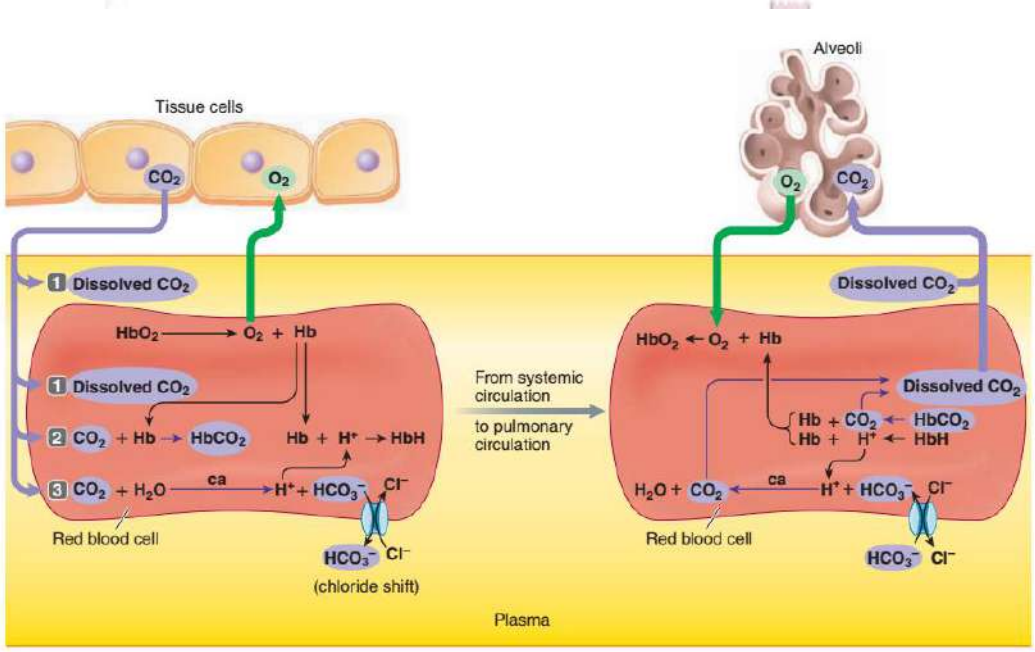
Hemoglobin has a much higher affinity for carbon monoxide than for O_2

- Hb's affinity for CO is 240 times that of its affinity for O_2, **carboxyhemoglobin (HBCO)**.
- Making Hb unavailable for O2 transport. Even though the Hb concentration and Po_2 are normal, the O_2 content of the blood is seriously reduced.
- CO is not a normal constituent of inspired air, produced during the incomplete combustion (burning) of carbon products such as automobile gasoline, coal, wood, and tobacco.
- CO is odorless, colorless, tasteless, and nonirritating, CO is not detectable. so, the victim has no sensation of breathlessness and makes no attempt to increase ventilation, even though the cells are O_2-starved.

Most CO_2 is transported in the blood as bicarbonate

- CO_2 is transported in the blood in three ways: (summarized in ***table 13-7***, ***fig. 13-31***)and (**animation 2**)

1. ***Physical dissolved.***
2. ***Bound to hemoglobin.***
3. ***As bicarbonate.***



ca = Carbonic anhydrase

▲ TABLE 13-6 Methods of Gas Transport in the Blood

Gas	Method of Transport in Blood	Percentage Carried in This Form
O_2	Physically dissolved	1.5
	Bound to hemoglobin	98.5
CO_2	Physically dissolved	10
	Bound to hemoglobin	30
	As bicarbonate (HCO_3^-)	60

1. ***Physical dissolved***, depends on the Pco_2, 10% of the blood's total CO_2 content.
2. ***Bound to hemoglobin***, 30% of the CO_2 combines with Hb to form ***corbamino hemoglobin*** **($HbCO_2$)**.
3. ***As bicarbonate*** **(HCO_3^-)**, 60% of the CO_2 being converted into HCO_3^- within the RBCs:

carbonic anhydrase

$$CO_2 + HO_2 \leftrightarrows \underset{\text{Carbonic acid}}{H_2CO_3} \leftrightarrows \underset{\text{Bicarbonate}}{H^+ + HCO_3^-}$$

- CO_2 molecule are thus present in the blood as HCO_3^-, because it is more soluble in the blood than CO_2.

Chloride shift: the red cell membrane has a HCO_3^--Cl^- carrier that passively facilitates the diffusion of HCO_3^-, but not H^+, diffuses down its concentration gradient, and chloride ions (Cl^-) down its electrical gradient to restore electric neutrality.

Haldane effect; the fact that removing O_2 from Hb increases the ability of Hb to pick up CO_2 and CO_2-generated H^+ . Reduced Hb has a greater affinity for H^+ than HbO_2 does. There fore, unloading O_2 facilitates Hb pickup of CO_2-generated H^+.

TABLE 13-7 Mini Glossary of Clinically Important Respiratory States

Apnea Transient cessation of breathing

Asphyxia O_2 starvation of tissues, caused by a lack of O_2 in the air, respiratory impairment, or inability of the tissues to use O_2

Cyanosis Blueness of the skin resulting from insufficiently oxygenated blood in the arteries

Dyspnea Difficult or labored breathing

Eupnea Normal breathing

Hypercapnia Excess CO_2 in the arterial blood

Hyperpnea Increased pulmonary ventilation that matches increased metabolic demands, as in exercise

Hyperventilation Increased pulmonary ventilation in excess of metabolic requirements, resulting in decreased P_{CO_2} and respiratory alkalosis

Hypocapnia Below-normal CO_2 in the arterial blood

Hypoventilation Underventilation in relation to metabolic requirements, resulting in increased P_{CO_2} and respiratory acidosis

Hypoxia Insufficient O_2 at the cellular level

- **Anemic hypoxia** Reduced O_2-carrying capacity of the blood
- **Circulatory hypoxia** Too little oxygenated blood delivered to the tissues; also known as stagnant hypoxia
- **Histotoxic hypoxia** Inability of the cells to use available O_2
- **Hypoxic hypoxia** Low arterial blood P_{O_2} accompanied by inadequate Hb saturation

Respiratory arrest Permanent cessation of breathing (unless clinically corrected)

Suffocation O_2 deprivation as a result of an inability to breathe oxygenated air

Abnormalities in arterial Pco_2

- **Hypercapnia** refers to excess CO_2 in arterial blood; it is caused by **hypoventilation**, with most lung diseases. CO_2 accumulation occurs concurrently with an O_2 deficit, (fig. 13-32) in pulmonary edema or emphysema, O_2 transfer suffers more than CO_2 transfer because the diffusion coefficient for CO_2 is 20 times that of O_2, hypoxic hypoxia occurs much more readily than hypercapnia.
- **Hypocapia**, is brought by hyper ventilation, when a person "overbreathes" the rate of ventilation is in excess of the body's metabolic needs for CO_2 removal. Triggered by anxiety states, fever, and aspirin poisoning, arterial Po_2 increases, because Hb is almost fully saturated at the normal arterial Po_2, very little additional O_2 is added to the blood.
- Increased ventilation that matches an increased metabolic demand, such as during exercise, is termed **hyperpnea**.

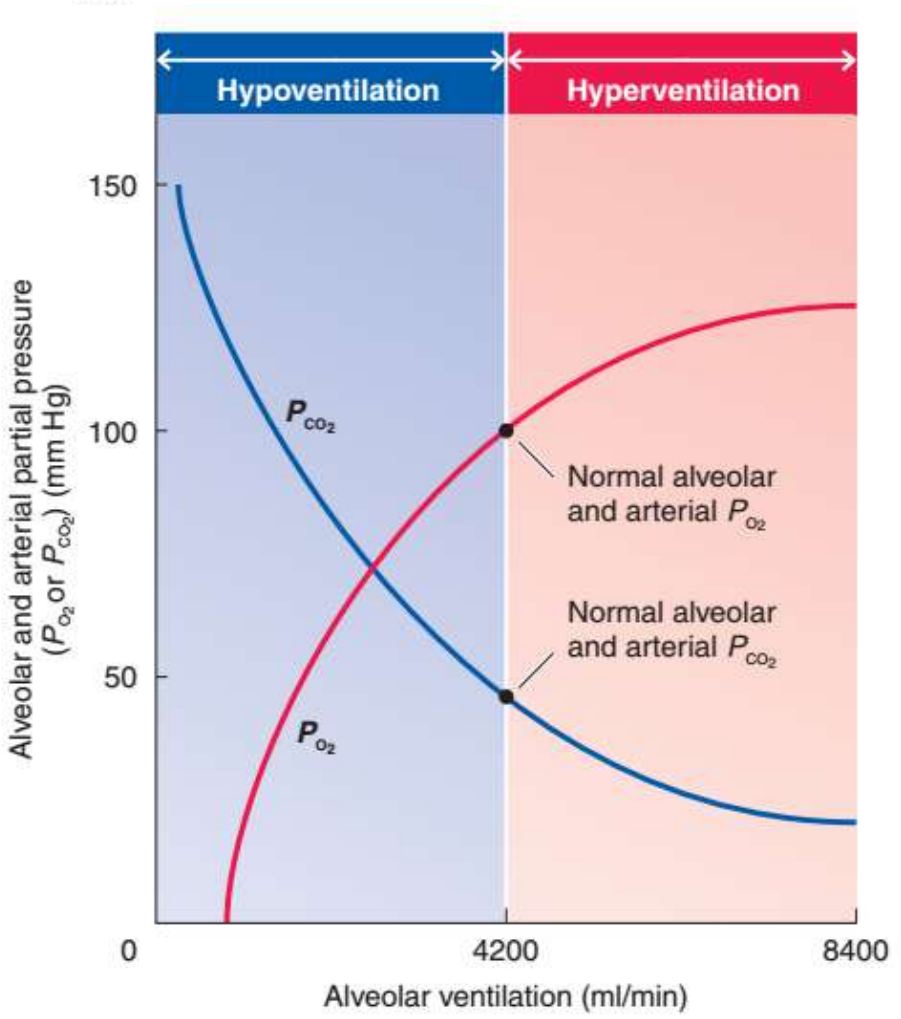


FIGURE 13-32 Effects of hyperventilation and hypoventilation on arterial P_{O_2} and P_{CO_2}.

Consequences of abnormalities in arterial blood gases

- The consequences of reduced O_2 availability to the tissues during hypoxia are apparent, to sustain energy-generating metabolic activities. The consequences of abnormal blood CO_2 levels are less obvious, primarily affect acid-base balance:

❶ Hypercapnia elevates production of carbonic acid, generation of excess H^+ produces an acidic condition termed ***respiratory acidosis***,

❷ and vice versa, the resultant alkalotic condition is called ***respiratory alkalosis***.

Control of respiration

- Similar to cardiovascular system, inspiratory muscles must rhythmically contract and relax to alternately fill the lungs with air and empty them, automatically without conscious effort. However, the mechanisms and control of these two systems are remarkably different.
- **Respiratory centers in the brain stem establish a rhythmic breathing pattern**
- The rhythmic pattern of breathing is established by cyclical neural activity to the respiratory muscles, is absolutely essential in maintaining breathing and in reflexly adjusting the level of ventilation to match changing needs for O_2 uptake and CO_2 removal. Respiratory activity can be voluntarily modified to accomplish speaking, singing, whistling, playing a wind instrument, or holding one's breath while swimming.

Components of neural control of respiration

(1) Factors responsible for generating the alternating inspiration-expiration rhythm, housed in the brain stem.

(2) Factors that regulate magnitude of ventilation, (rate and depth of breathing), to match body needs, and

(3) Factors that modify respiratory activity to serve other purposes, it may by either voluntary, as in a cough or sneeze.

The primary respiratory control center, the *medullary respiratory center*, consists of several aggregations of neuronal cell bodies provide output to the respiratory muscles. Two other respiratory centers in the brain stem in the pons: the ***apneustic center*** and ***pneumotaxic center***, influence output from the medullary respiratory center (fig. 13-33).

How these regions interact to establish respiratory rhythmicity ***???*** ➲

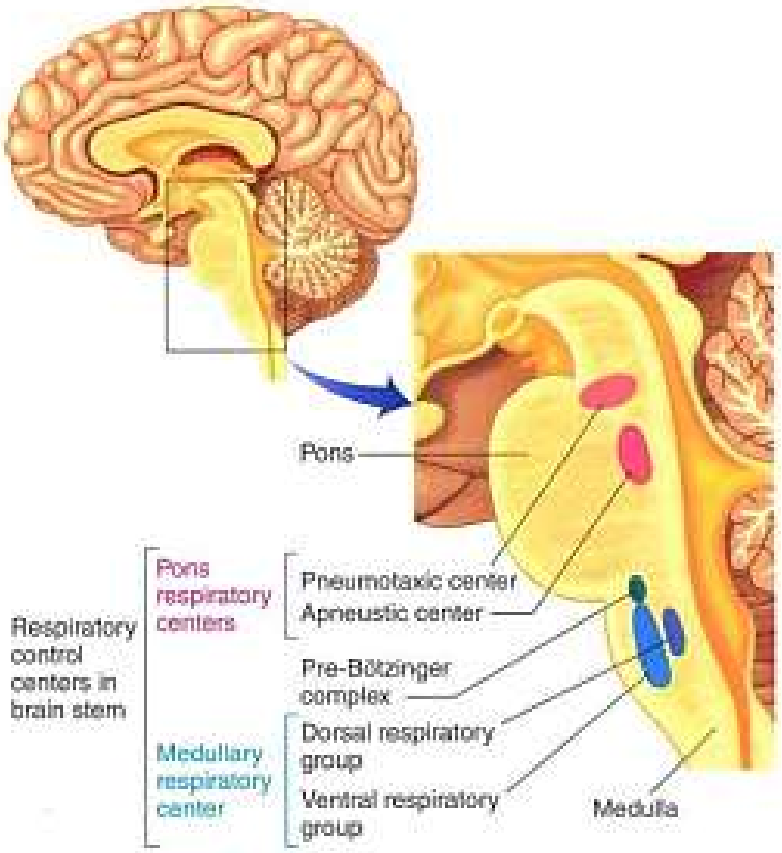


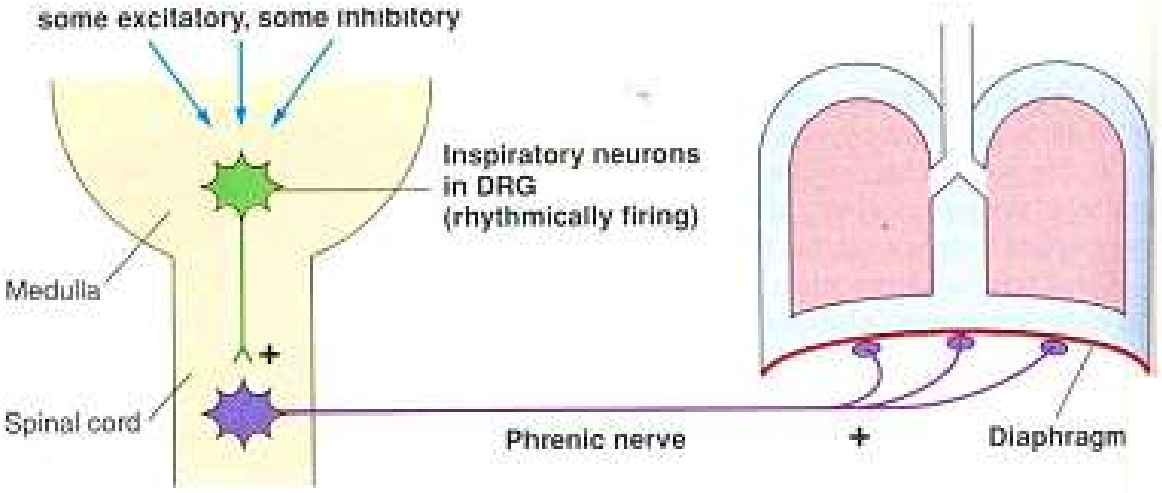
FIGURE 13-33
Respiratory control centers in the brain stem

➢Inspiratory and expiratory neurons in the medullary center

- Impulses originating in the medullary center (fig. 13-34), in turn stimulate the inspiratory muscles, leading to inspiration; when these neurons are not firing, the inspiratory muscles relax, and expiration takes place.
- The **medullary respiratory center** consists of two neuronal clusters:

(1) the **dorsal respiratory group (DRG)** a respiratory neurons whose supply the inspiratory muscles.

(2) the **ventral respiratory group (VRG)** is inspiratory neurons and expiratory neurons, called into play by the DRG as an "overdrive" mechanism during periods when demands for ventilation are increased, especially important in active expiration, supplying the expiratory muscles.



● FIGURE 13-34

Schematic representation of medullary dorsal respiratory group (DRG) control of inspiration
Inspiration takes place when the inspiratory neurons are firing and activating the motor neurons that supply the inspiratory muscles. Expiration takes place when the inspiratory neurons cease firing, so that the motor neurons supplying the inspiratory muscles are no longer activated.

Generation of respiratory rhythm

- The basic rhythm of ventilation now widely believed to lie in the **preBötzinger complex**. A network of neurons in this region display pacemaker activity, similar to the SA node.
- **Influences from the pneumotaxic and apneustic centers**
- The pontine centers exert "fine-tuning" influences over the medullary center to help produce normal. The **pneumotaxic center** limiting the duration of inspiration, in contrast, the **apneustic center** providing an extra boost to the inspiratory drive.
- Without the pneumotaxic brakes, prolonged inspiratory gasps abruptly interrupted by very brief expiration, known as **apneusis**, occurs in certain types of severe brain damage.
- **Hering-Breuer reflex**, is triggered to prevent overinflation of the lungs.
- **Pulmonary stretch receptors** located within the smooth muscle layer of the airways are activated by the stretching of the lungs at large tidal volumes. Action potentials travel to the medullary center and inhibit the inspiratory neurons. This negative feedback from the highly stretched lungs themselves helps cut inspiration short before the lungs overinflated.

The magnitude of ventilations adjusted in response to three chemical factors: Po_2, Pco_2, and H^+

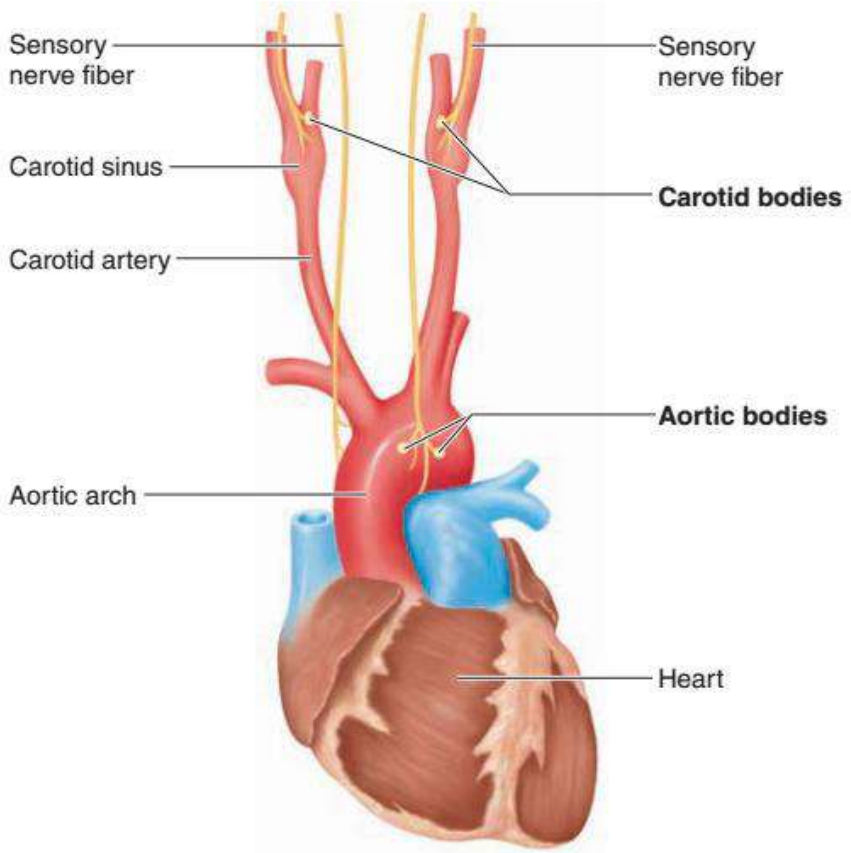
- Arterial blood gases are maintained within normal range by varying magnitude of ventilation (rate and depth of breathing) to match the body's needs for O_2 uptake and CO_2 removal.
- The medullary respiratory center receives inputs that provide information about the body's needs for gas exchange. It responds by sending appropriate signals to the motor neurons supplying the respiratory muscles, to adjust the rate and depth of ventilation to meet those needs, decreased arterial Po_2 or increased arterial Pco_2.
- These two factors influence the magnitude of ventilation, but not to the same pathway. Also, H^+ influences the level of respiratory activity.

▲ TABLE 13-8 Influence of Chemical Factors on Respiration

Chemical Factor	Effect on the Peripheral Chemoreceptors	Effect on the Central Chemoreceptors
↓ P_{O_2} in the Arterial Blood	Stimulates only when the arterial P_{O_2} has fallen to the point of being life threatening (< 60 mm Hg); an emergency mechanism	Directly depresses the central chemoreceptors and the respiratory center itself when < 60 mm Hg
↑ P_{CO_2} in the Arterial Blood (↑ H^+ in the Brain ECF)	Weakly stimulates	Strongly stimulates; is the dominant control of ventilation (Levels > 70–80 mm Hg directly depress the respiratory center and central chemoreceptors)
↑ H^+ in the Arterial Blood	Stimulates; important in acid–base balance	Does not affect; cannot penetrate the blood–brain barrier

Decreased arterial Po_2 increases ventilation only as an emergency mechanism

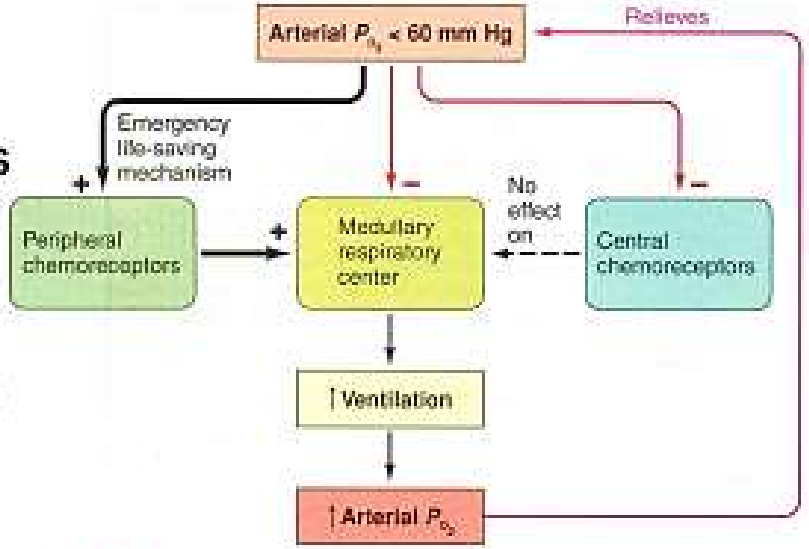
- Arterial Po_2 is monitored by **peripheral chemoreceptors** known as the **carotid bodies** and **aortic bodies**, (fig. 13-35) distinctly different from baroreceptors that monitor pressure.



● **FIGURE 13-34 Location of the peripheral chemoreceptors.** The carotid bodies are located in the carotid sinus, and the aortic bodies are located in the aortic arch.

Effect of a large decrease in Po_2 on the peripheral chemoreceptors

- Arterial Po_2 does not play a role in the normal ongoing regulation of respiration, because Hb is still 90% saturated at an arterial Po_2 of 60 mm Hg, but the % Hb saturation drops precipitously when the Po_2 falls below this level, this reflex mechanism is a lifesaver (fig. 13-36). Because the peripheral chemoreceptors respond to the Po_2 of the blood, *not* the total O_2 content of the blood, it can be reduced in anemic states, or in CO poisoning. In both cases, arterial Po2 is normal, so respiration is not stimulated.



● FIGURE 13-36
Effect of threateningly low arterial P_{O_2} (<60 mm Hg) on ventilation

Direct effect of a large decrease in Po_2 on the respiratory center

- Direct depression of the respiratory center by the markedly low arterial Po_2 would further reduce ventilation, until ventilation ceased and death occurred.

CO_2-generated H^+ in the brain is normally the primary regulator of ventilation

- Because changes in alveolar ventilation have an immediate and pronounced effect on arterial Pco_2. an increase in arterial Pco_2 reflexly stimulates the respiratory center, with the resultant increase in ventilation promoting elimination of the excess CO_2 to the atmosphere, and vice versa.

Effect of increased Pco_2 on the central chemoreceptors

- The carotid and aortic bodies play only a minor role in reflexly stimulating ventilation in response to elevation in arterial Pco_2, the **central chemoreceptors,** do not monitor CO_2 itself; however, they are sensitive to changes in CO_2-induced H^+ concentration in the brain extracellular fluid (ECF).
- According to the reaction:

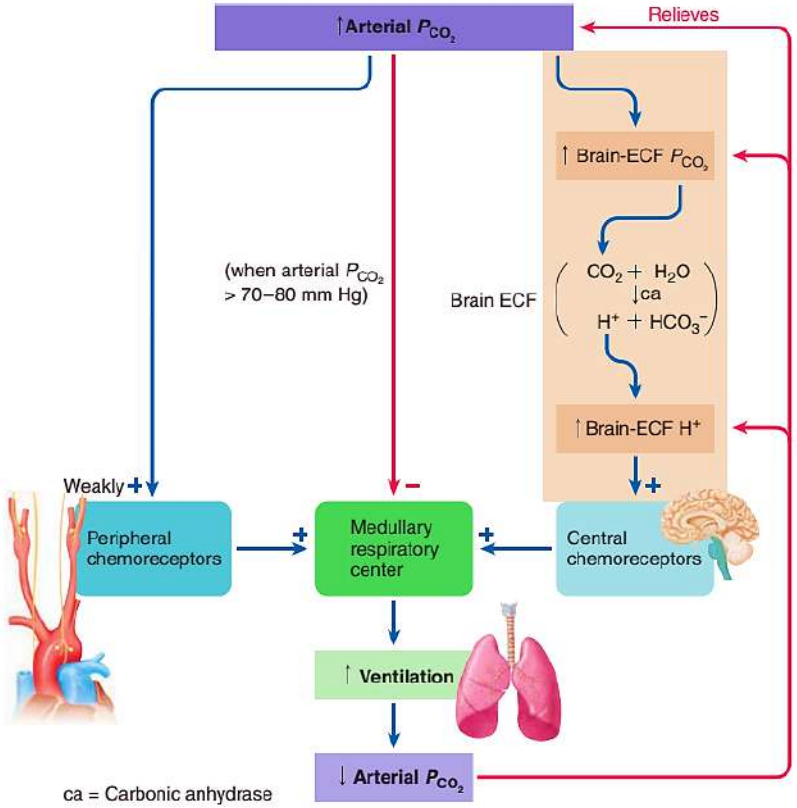
$$CO_2 + HO_2 \underset{\text{carbonic anhydrase}}{\leftrightarrows} \underset{\text{Carbonic acid}}{H_2CO_3} \leftrightarrows \underset{\text{Bicarbonate}}{H^+ + HCO_3^-}$$

- Which in turn increase ventilation by stimulating the respiratory center through synaptic connections, and vice versa (fig. 13-37).

- H^+ is not readily able to permeate the blood-brain barrier, so the central chemoreceptors are responsive only to H^+ generated within the brain ECF itself as a result of CO_2 entry.
- The powerful influence of the central chemoreceptors on the respiratory center is responsible for your inability to deliberately hold your breath for more than about a minute. Breathing resumes long before arterial Po_2 falls to the threateningly low levels that trigger the peripheral chemoreceptors.

Direct effect of a large increase in Pco_2 on the respiratory center

- Very high levels of CO_2 directly depress the entire brain, including the respiratory center, just as very low levels of O_2 do.
- Co_2 must be removed and O_2 supplied in closed environments such as closed-system anesthesia machines, submarines, or space capsules, CO_2 could reach lethal levels, not only because it depresses respiration but also because it produces severe respiratory acidosis.



● **FIGURE 13-35** Effect of increased arterial P_{CO_2} on ventilation.

Loss of sensitivity to Pco_2 with lung disease

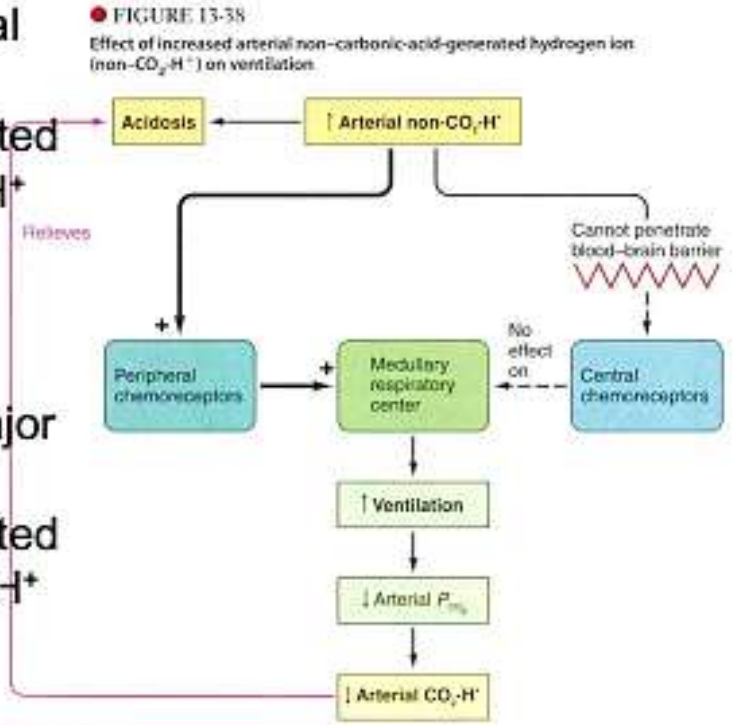
- The elevated Pco_2 (acting via the central chemoreceptors) and the reduced Po_2 (acting via the peripheral chemoreceptors) are *synergistic;* that is, the combined stimulatory effect on respiration exerted by these two inputs together is greater than the sum of their independent effects.
- Some patients with severe chronic lung disease lose their sensitivity to an elevated arterial Pco_2, enough HCO_3^- may cross the blood-brain barrier to buffer, or "neutralize," the excess H^+.
- In these patients, the hypoxic drive to ventilation becomes their primary respiratory stimulus. Ironically, administering O_2 to such patients to relieve the hypoxic condition can markedly depress their drive to breathe by elevating the arterial Po_2 and removing the primary driving stimulus for respiration.

Adjustments in ventilation in response to changes in arterial H^+ are important in acid-base balance

Changes in arterial H^+ concentration cannot influence the central chemoreceptors, because H^+ does not readily cross the blood-brain barrier.

These CO_2-induced H^+ changes in the arterial blood are detected by the peripheral chemoreceptors; the result is reflexly stimulated ventilation in response to increased arterial H^+ concentration and depressed ventilation in association with decreased arterial H^+ concentration.

The peripheral chemoreceptors do play a major role in adjusting ventilation in response to alterations in arterial H^+ concentration unrelated to fluctuations in Pco_2. For example, arterial H^+ increases during diabetes mellitus because excess H^+-generating keto acids, reflexly stimulates ventilation by means of the peripheral chemoreceptors , and vice versa (fig. 13-38).



الحمد لله رب العالمين