### **Respiratory physiology**

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Compilation

The function of the **respiratory system** is to deliver air to the lungs. Oxygen in the air diffuses out of the lungs and into the blood, while carbon dioxide diffuses in the opposite direction, out of the blood and into the lungs. Respiration includes the following processes:

- Pulmonary ventilation is the process of breathing—inspiration (inhaling air) and expiration (exhaling air).
- External respiration is the process of gas exchange between the lungs and the blood. Oxygen diffuses into the blood, while CO<sub>2</sub> diffuses from the blood into the lungs.
- Gas transport, carried out by the cardiovascular system, is the process of distributing the oxygen throughout the body and collecting CO<sub>2</sub> and returning it to the lungs.
- Internal respiration is the process of gas exchange between the blood, the interstitial fluids (fluids surrounding the cells), and the cells. Inside the cell, cellular respiration generates energy (ATP), using O<sub>2</sub> and glucose and producing waste CO<sub>2</sub>.

## Primary Function of the Lung



- Bring in oxygen for delivery to tissues and remove carbon dioxide from blood
- Accomplished through tidal breathing
  - Inspired, fresh air is distributed via the airways to the gas exchanging regions or alveoli
  - Oxygen depleted, carbon dioxide containing gas is exhaled via same airways
- Air, like any gas or fluid, moves from areas of higher pressure to lower pressure

- External respiration:
  - exchange of O2 & CO2 between external environment & the cells of the body
  - efficient because alveoli and capillaries have very thin walls & are very abundant (your lungs have about 300 million alveoli with a total surface area of about 75 square meters)
- Internal respiration intracellular use of O2 to make ATP
- occurs by simple diffusion along partial pressure gradients

### What is Partial Pressure?:

- it's the individual pressure exerted independently by a particular gas within a mixture of gasses. The air we breath is a mixture of gasses: primarily nitrogen, oxygen, & carbon dioxide. So, the air you blow into a balloon creates pressure that causes the balloon to expand (& this pressure is generated as all the molecules of nitrogen, oxygen, & carbon dioxide move about & collide with the walls of the balloon). However, the total pressure generated by the air is due in part to nitrogen, in part to oxygen, & in part to carbon dioxide. That part of the total pressure generated by oxygen is the 'partial pressure' of oxygen, while that generated by carbon dioxide is the 'partial pressure' of carbon dioxide. A gas's partial pressure, therefore, is a measure of how much of that gas is present (e.g., in the blood or alveoli).
- the partial pressure exerted by each gas in a mixture equals the total pressure times the fractional composition of the gas in the mixture. So, given that total atmospheric pressure (at sea level) is about 760 mm Hg and, further, that air is about 21% oxygen, then the partial pressure of oxygen in the air is 0.21 times 760 mm Hg or 160 mm Hg.



# Spirogram Showing Lung Volumes and Capacities

### what you need to know

### **Lung Volumes and Capacities**

### The following terms describe the various lung (respiratory) volumes:

• The tidal volume (TV), about 500 ml, is the amount of air inspired during normal, relaxed breathing.

- The inspiratory reserve volume (IRV), about 3,100 ml, is the additional air that can be forcibly inhaled after the inspiration of a normal tidal volume.
- The expiratory reserve volume (ERV), about 1,200 ml, is the additional air that can be forcibly exhaled after the expiration of a normal tidal volume.
- Residual volume (RV), about 1,200 ml, is the volume of air still remaining in the lungs after the expiratory reserve volume is exhaled.

### Summing specific lung volumes produces the following lung capacities:

- The total lung capacity (TLC), about 6,000 ml, is the maximum amount of air that can fill the lungs (TLC = TV + IRV + ERV + RV).
- The vital capacity (VC), about 4,800 ml, is the total amount or air that can be expired after fully inhaling (VC = TV + IRV + ERV = approximately 80% TLC).
- The inspiratory capacity (IC), about 3,600 ml, is the maximum amount of air that can be inspired (IC = TV + IRV).
- The functional residual capacity (FRC), about 2,400 ml, is the amount of air remaining in the lungs after a normal expiration (FRC = RV + ERV).

Some of the air in the lungs does not participate in gas exchange. Such air is located in the anatomical dead space within bronchi and bronchioles—that is, outside the alveoli.



### Lung Volumes and Capacities

A. Volumes are measured by spirometry except for residual volume and any volumes containing residual volume.

1. Tidal volume (VT) is the volume of air that moves into and out of the lung in each breath. Tidal volume is usually about 500 mL.

2. Inspiratory reserve volume (IRV) is the volume of air that can be inspired with maximum inspiratory effort, starting at the end of a normal inspiration. IRV is 2–3 L.

**3. Expiratory reserve volume** (**ERV**) is the volume of air that can be expired with maximum expiratory effort, starting at the end of a normal expiration. ERV is **about 1.5 L.** 

**4. Residual volume** (**RV**) is the volume of air remaining in the lungs (alveolar and dead space) after a maximum expiration. RV is about 1.5 L. RV cannot be measured from a simple spirometer record, because the **spirometer measures** only **changes in lung volume** and not the absolute amount of air in the lung.

**5. Functional reserve capacity** (**FRC**) is the volume of air in the lungs at the end of a normal passive expiration (FRC = ERV + RV).

6. Inspiratory capacity (IC) is the maximum volume of air that can be inspired from the FRC (IC = VT + IRV).

**7. Vital capacity** (VC) is the maximum volume of air that can be expired after a maximal inspiration (VC = ERV + VT + IRV).

**8. Total lung capacity** (**TLC**) is the volume of air in the lung system after a maximal inspiration (TLC = RV + ERV + VT + IRV).

# Breathing – Changes in Lung Volume



B. Ventilation is the process that involves movement of air through the airways and into the alveoli.

**1. Total ventilation**, also called **minute ventilation**, *V* **E**, is defined as the volume of air entering and leaving the lungs per minute. Minute ventilation

is equal to the tidal volume times the number of breaths per minute (average = 12/min).

**2.** Total ventilation, however, does not represent the inspired air that is available for gas exchange, because of the effect of the anatomic dead space.

**3.** The **anatomic dead space** (**VD**) includes the **conducting zone** (airways that do not participate in gas exchange) that ends at the level of the terminal bronchioles. VD averages 150 mL.

4. Alveolar ducts and alveolar sacs make up the **respiratory zone**, where significant gas exchange with blood occurs.

5. At the end of expiration, the anatomic dead space contains air that has come from the alveoli.

6. During the initial phase of inspiration, inspired air flows into the conducting zone, and anatomic dead space gas moves into the alveoli.

7. At the end of inspiration, the anatomic dead space is filled with humidified atmospheric air.

**8. With each tidal volume,** the volume of new air reaching the alveoli is VT \_ VD. Similarly, the volume of alveolar air expelled with each breath is VT \_ VD.

9. Alveolar ventilation (V A) is defined as the total volume of alveolar air expired per minute. For example,

$$\dot{V}_{A} = (V_{T} - V_{D}) \times (breathing frequency)$$
  
= (500 mL - 150 mL) × 12 = 4200 mL/min

a. Increasing the depth of breathing by 200 mL increases the total and alveolar ventilation by 200 mL.

**b.** Increasing the rate of breathing will cause a greater increase in total ventilation than in alveolar ventilation.

**10.** Forced vital capacity (FVC) is the volume of air that can be forcibly expired after a maximal inspiration.

**11. Forced expiratory volume** (**FEV1**) is the volume of air (normally around 80%) that can be expired in 1 second after a maximal inspiration.

a. The FEV1/FVC ratio is a pulmonary function test used to diagnose obstructive (eg, asthma) and restrictive (eg, fibrosis) disorders.

**b.** FEV1 and FVC are decreased in fibrosis, whereas the FEV1/FVC ratio is decreased in asthma.

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**Figure 3–1.** Subdivisions of lung volumes. The spirometry record shows an idealized summary of changes in lung volume during normal breathing, maximal inspiration, maximal expiration, and a maximal inspiration followed by a full expiration to the residual volume known as vital capacity (VC). The RV and FRC cannot be measured by spirometry. ERV, expiratory reserve volume; FRC, functional reserve capacity; IC, inspiratory capacity; IRV, inspiratory reserve volume; TLC, total lung capacity.

### **II. Muscles of Breathing**

### **A. Inspiration**

- 1. The **diaphragm** is the major muscle of inspiration.
- a. This dome-shaped muscle is located between the thorax and the abdomen.
- b. It is innervated by phrenic nerves.
- c. The diaphragm moves down during inspiration and up during expiration.
- d. Quiet breathing is accomplished almost entirely by the diaphragm.







**2. External intercostals** are important muscles for active inspiration, for example, during exercise, singing, playing wind instruments, and sighing.

**a.** These muscles are located between the ribs and are oriented such that contraction elevates the ribs and increases thickness of the thoracic cage, thereby drawing air into the lungs.

**b.** They are innervated by intercostal nerves that come from the spinal cord at the level of the rib attached to a given intercostal muscle.

### 3. The accessory inspiratory muscles are:

- the scalene
- sternomastoid muscles
- the alae nasi (used in nostril flaring).



### **B. Expiration**

1. The muscles of expiration are passive during quiet breathing and active during exercise.

**2.** The **abdominals** are the main muscles of expiration. Contraction of these muscles opposes the action of the diaphragm, that is, tending to push the diaphragm upward.

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**3.** The **internal intercostals** oppose action on the external intercostals. They are oriented so that contraction tends to pull the rib cage down and decreases the anterior-posterior thickness of the thorax.





### Mechanics of Breathing

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**Boyle's law** describes the relationship between the pressure (P) and the volume (V) of a gas. The law states that if the volume increases, then the pressure must decrease (or vice versa). This relationship is often written algebraically as PV= constant, or  $P_1V_1 = P_2V_2$ . Both equations state that the product of the pressure and volume remains the same. (The law applies only when the temperature does not change.)

Breathing occurs when the contraction or relaxation of muscles around the lungs changes the total volume of air within the air passages (bronchi, bronchioles) inside the lungs. When the volume of the lungs changes, the pressure of the air in the lungs changes in accordance with Boyle's law. If the pressure is greater in the lungs than outside the lungs, then air rushes out. If the opposite occurs, then air rushes in. Here is a summary of the process:

- Inspiration occurs when the inspiratory muscles-that is, the diaphragm and the external intercostals musclescontract. Contraction of the diaphragm (the skeletal muscle below the lungs) causes an increase in the size of the thoracic cavity, while contraction of the external intercostals muscles elevates the ribs and sternum. Thus, both muscles cause the lungs to expand, increasing the volume of their internal air passages. In response, the air pressure inside the lungs decreases below that of air outside the body. Because gases move from regions of high pressure to low pressure, air rushes into the lungs.
- Expiration occurs when the diaphragm and external intercostal muscles relax. In response, the elastic fibers in lung tissue cause the lungs to recoil to their original volume. The pressure of the air inside the lungs then increases above the air pressure outside the body, and air rushes out. During high rates of ventilation, expiration is facilitated by contraction of the expiratory muscles (the intercostals muscles and the abdominal muscles).

Lung compliance is a measure of the ability of the lungs and thoracic cavity to expand. Due to the elasticity of lung tissue and the low surface tension of the moisture in the lungs (from the surfactant), the lungs normally have high compliance.

### **Pulmonary Ventilation**

A) Inspiration

1) Boyle's Law: air pressure in closed space inversely correlated with volume
a) increase volume == decrease pressure; decrease volume == increase pressure
2) differences in air pressure between air and lungs drives movement of air into/out of lungs
3) normal inspiration is an ACTIVE process
4) inspiratory muscles involved:
a) diaphragm (75% normal inspiratory action)
i) activated by phrenic nerve
ii) contraction causes diaphram to "flatten"
iii) a 1cm drop in the diaphram decreases pulmonary air pressure 1-3mmHg
iv) this drop in pulmonary air pressure causes approx 0.5L air to move into lungs
b) external intercostals (25% normal inspiratory action)
i) activated by intercostal nerves
c) accessory muscles can also enhance inspiration
i) sternocleidomastoid and scalenes
5) normal breathing ("eupnea") consists of moving approx 0.51 (tidal volume) into/out of lungs
6) not all air inspired actually enters lung
a) anatomic "dead space" (approx 150ml) includes LIRT and trachea & bronchi
b) ONLY air within alveoli (approx 350ml) can exchange gases
B) Expiration
1) expiration is a passive process
2) relaxation of dianhradm and external intercostals
a) ribs are depressed and diaphragm curves upwards
3) expiration can become active process by contraction of abdominals and internal intercostals
4) major factors driving expiration:
a) elastic recoil of lungs
b) surface tension of alveolar fluid (lessened by surfactant)
5) these factors create high "compliance"
a) compliance refers to ease of lung expansion
b) low compliance from pulmonary scarring, edema, surfactant deficiency (especially in premature babies)
c) compliance too high in emphysema
C) Intranleural pressure
1) pleural cavity pressure MUST stay approx 4mmHq LESS than intrapulmonary pressure
2) any condition that equalizes intraneural and intranulmonary pressures causes immediate lung collapse
a) chest trauma may runture visceral niura leading to atelectasis ("collansed lung")
b) collapsed lung is useless for ventilation - can not inspire
c) "pneumothorax" refers to air in intranleural space, will prevent lung ventilation
d) each lung is in a completely separate pleural cavity, so pneumothoray of one lung does not affect the other
D) Breathing natterns/deficits
1) eunnea - normal breathing pattern (11-15 hpm)
2) dyspnea - nainful difficult breathing
3) hypoxia - decrease oxygen delivery to tissues
4) hypercannia - increase carbon dioxide levels in blood
Gas Exchange (external & internal respiration)
A) CO2 and O2 gas exchange
1) Dalton's Law: (concerns pressure of specific gases in mixtures)
a) pressure of specific gas in a mixture determined by % of that gas in the mixture
i) [total atm, pressure] x [gas %] = partial pressure of that gas
b) 760mmHa x 21%O2 = $Po2(160mmHa)$
c) 760mmHa x 0.04%CO2 = $Pco2(0.3mmHa)$
d) 760mmHa x 78.6%N2 = $Pn2(597mmHa)$
e) ** it is the partial pressure of each gas that determines "direction" of diffusion of each gas **
B) Partial Pressures of blood gases
1) atmosphere: Po2=160mmHq, Pco2=0.3mmHq
2) alveolar air: Po2=105mmHq, Pco2=40mmHq
3) oxygenated blood: Po2=100mmHg, Pco2=40mmHg

- 4) tissues: Po2=40mmHg, Pco2=45mmHg
  5) deoxygenated blood: Po2=40mmHg, Pco2=45mmHg
  6) \*\* why less P02 in alveoli than atmosphere
  C)Rate of gas diffusion dependant on:

1) partial pressure

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### C. Forces Acting on the Lungs

- 1. Lung recoil refers to forces that develop in the lung wall during expansion.
- a. Recoil increases as the lung enlarges.
- b. Recoil always acts to collapse the lung.

**2. Intrapleural pressure** (also called pleural pressure, or **PPL**) is the pressure in the thin film of fluid between the lung and chest wall (Figure 3–2).

- a. PPL is generally subatmospheric (~ -5 cm H20).
- b. Negative subatmospheric pressures act to expand the lung, whereas positive pressures act to collapse the lung.
- c. When PPL exceeds recoil forces the lungs expand.
- d. When recoil forces exceed PPL the lungs decrease in volume.
- 3. Alveolar pressure (PA) is the pressure of the alveolar air (see Figure 3–2).
- a. PA drives airflow into and out of the lungs.
- **b.** If PA equals 0 (ie, no airflow), then PA is the same as atmospheric pressure.
- c. PA is less than 0 during respiration; PA is greater than 0 during expiration.

**4. Transpulmonary pressure** (**PTP**) is the difference between the pressure inside the lung (alveolar pressure) and the pressure outside the lung (intrapleural pressure). PTP determines the degree of inflation of the lung.

- 5. Pneumothorax is the presence of air in the pleural space.
- a. If the chest is opened, the intrapleural pressure changes to equal atmospheric pressure.
- b. Lung recoil decreases to zero as the lung collapses.
- c. The chest wall expands.
- III. Lung Compliance
- A. Compliance (CL) is the stretching of the lungs and is calculated as follows

$$C_{\rm L} = \frac{\Delta V}{P_{\rm TP}},$$

where

 $\Delta V$  = change in lung volume

*P*TP = transpulmonary pressure

**B.** Compliance is the change in lung volume per unit change in airway pressure. For example,

$$C_{\rm L} = \frac{\Delta V}{\Delta_{P_{\rm TP}}} = \frac{1000 \text{ mL}}{5 \text{ cm H}_2 \text{O}} = 200 \text{ mL/ cm H}_2 \text{O}$$

C. High CL means more air will flow for a given change in pressure.









**Figure 3–2.** Alveolar and intrapleural pressures during normal breathing. Intrapleural pressure remains negative during inspiration and expiration. Alveolar pressure is negative during inspiration and positive during expiration.

E. If PTP becomes more negative, more air will flow into the system, and if PTP becomes more positive more air will flow out of the system.

F. CL is an indicator of the effort required to expand the lungs to overcome recoil.

G. Compliant lungs have low recoil, whereas stiff lungs have a large recoil force

**H.** The **pressure-volume curve** is not the same for inspiration and expiration; this difference is called **hysteresis**, which is due primarily to the effects of airway resistance.

### **IV. Components of Lung Recoil**

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A. The collagen and elastic fibers of the lung tissue provide elastance, which is the reciprocal of compliance.

**B.** Surface tension forces created whenever a liquid-air interface is present in the fluid lining the alveoli act to collapse the alveoli and contribute to lung recoil.

1. The fluid lining the alveoli contains **surfactant**, a surface-tension–lowering agent.

2. Surfactant has three main functions.

a. It lowers surface tension forces in the alveoli, which reduces lung recoil and increases compliance.

b. The reduction in surface tension forces in small alveoli decreases their tendency to collapse.

c. It also reduces capillary filtration forces, which decreases the risk of pulmonary edema.



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Surfactant is a complex substance containing phospholipids and a number of apoproteins. This essential fluid is produced by the Type II alveolar cells, and lines the alveoli and smallest bronchioles. Surfactant reduces surface tension throughout the lung, thereby contributing to its general compliance. It is also important because it stabilizes the alveoli. LaplaceÕs Law tells us that the pressure within a spherical structure with surface tension, such as the alveolus, is inversely proportional to the radius of the sphere (P=4T/r for a sphere with two liquid-gas interfaces, like a soap bubble, and P=2T/r for a sphere with one liquid-gas interface, like an alveolus: P=pressure, T=surface tension, and r=radius). That is, at a constant surface tension, small alveoli will generate bigger pressures within them than will large alveoli. Smaller alveoli would therefore be expected to empty into larger alveoli as lung volume decreases. This does not occur, however, because surfactant differentiallyreduces surface tension, more at lower volumes and less at higher volumes, leading to alveolar stability and reducing the likelihood of alveolar collapse.

Surfactant is formed relatively late in fetal life; thus premature infants born without adequate amounts experience respiratory distress and may die.

V. Airway Resistance
 A. The rate of airflow for a given driving pressure depends on airway resistance:

$$V = \frac{P_A}{R},$$

where V = flow rate (L/s) PA = alveolar pressure (mm Hg) R = airway resistance (R units)The more negative the intrapleural pressure (eg, during inspiration), the lower the airway resistance.

### B. According to Poiseuille's equation,

resistance 
$$\propto \frac{1}{r^4}$$
,

where r = radius of the airway Thus, a strong relationship exists between resistance and the radius of the airway.

Indications for referral to a pulmonary function laboratory:

- 1. Medical Diagnostic
- 2. Surgical Diagnostic
- 3. Disability Evaluation
- 4. Public Health
- 5. Research

### C. The following factors influence airway resistance:

1. Stimulation of parasympathetic nerves produces bronchoconstriction.

2. Stimulation of sympathetic nerves or circulating catecholamine produces bronchodilation.

3. Low lung volumes are associated with increased airway resistance, whereas high lung volumes are associated with decreased resistance.

**4.** Breathing a **high-density gas increases resistance** to airflow, whereas breathing a low-density gas decreases resistance to airflow.

5. The first and second (ie, medium-sized) bronchi represent most of the airway resistance.



**Partial Pressures of O<sub>2</sub> and CO<sub>2</sub> in the body** (normal, resting conditions):

- Alveoli
  - PO2 = 100 mm Hg
  - PCO<sub>2</sub> = 40 mm Hg
- Alveolar capillaries
  - Entering the alveolar capillaries
    - PO<sub>2</sub> = 40 mm Hg (relatively low because this blood has just returned from the systemic circulation & has lost much of its oxygen)
    - PCO<sub>2</sub> = 45 mm Hg (relatively high because the blood returning from the systemic circulation has picked up carbon dioxide)



• FIGURE 23-20 An Overview of Respiratory Processes and Partial Pressures in Respiration. (a) Partial pressures and diffusion at the respiratory membrane. (b) Partial pressures and diffusion in other tissues.



While in the alveolar capillaries, the diffusion of gasses occurs: oxygen diffuses from the alveoli into the blood & carbon dioxide from the blood into the alveoli.

o Leaving the alveolar capillaries

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- PO<sub>2</sub> = 100 mm Hg
- PCO<sub>2</sub> = 40 mm Hg

Blood leaving the alveolar capillaries returns to the left atrium & is pumped by the left ventricle into the systemic circulation. This blood travels through arteries & arterioles and into the systemic, or body, capillaries. As blood travels through arteries & arterioles, no gas exchange occurs.

- Entering the systemic capillaries
  - PO2 = 100 mm Hg
  - PCO<sub>2</sub> = 40 mm Hg
- Body cells (resting conditions)
  - PO<sub>2</sub> = 40 mm Hg
  - PCO2 = 45 mm Hg

Because of the differences in partial pressures of oxygen & carbon dioxide in the systemic capillaries & the body cells, oxygen diffuses from the blood & into the cells, while carbon dioxide diffuses from the cells into the blood.

- Leaving the systemic capillaries
  - PO<sub>2</sub> = 40 mm Hg
  - PCO<sub>2</sub> = 45 mm Hg

Blood leaving the systemic capillaries returns to the heart (right atrium) via venules & veins (and no gas exchange occurs while blood is in venules & veins). This blood is then pumped to the lungs (and the alveolar capillaries) by the right ventricle.

How are oxygen & carbon dioxide transported in the blood?

- Oxygen is carried in blood:
  - 1 bound to hemoglobin (98.5% of all oxygen in the blood)
  - 2 dissolved in the plasma (1.5%)

Because almost all oxygen in the blood is transported by hemoglobin, the relationship between the concentration (partial pressure) of oxygen and hemoglobin saturation (the % of hemoglobin molecules carrying oxygen) is an important one.

### Hemoglobin saturation:

- extent to which the hemoglobin in blood is combined with O2
- depends on PO2 of the blood:



The relationship between oxygen levels and hemoglobin saturation is indicated by the **oxygen-hemoglobin dissociation** (saturation) curve (in the graph above). You can see that at high partial pressures of O2 (above about 40 mm Hg),

hemoglobin saturation remains rather high (typically about 75 - 80%). This rather flat section of the oxygen-hemoglobin dissociation curve is called the 'plateau.'

Recall that 40 mm Hg is the typical partial pressure of oxygen in the cells of the body. Examination of the oxygenhemoglobin dissociation curve reveals that, under resting conditions, only about 20 - 25% of hemoglobin molecules give up oxygen in the systemic capillaries. This is significant (in other words, the 'plateau' is significant) because it means that you have a substantial reserve of oxygen. In other words, if you become more active, & your cells need more oxygen, the blood (hemoglobin molecules) has lots of oxygen to provide

When you do become more active, partial pressures of oxygen in your (active) cells may drop well below 40 mm Hg. A look at the oxygen-hemoglobin dissociation curve reveals that as oxygen levels decline, hemoglobin saturation also declines - and declines precipitously. This means that the blood (hemoglobin) 'unloads' lots of oxygen to active cells - cells that, of course, need more oxygen.



### Factors that affect the Oxygen-Hemoglobin Dissociation Curve:

The oxygen-hemoglobin dissociation curve 'shifts' under certain conditions. These factors can cause such a shift:

- lower pH
- increased temperature
- more 2,3-diphosphoglycerate
- increased levels of CO2

These factors change when tissues become more active. For example, when a skeletal muscle starts contracting, the cells in that muscle use more oxygen, make more ATP, & produce more waste products (CO2). Making more ATP means releasing more heat; so the temperature in active tissues increases. More CO2 translates into a lower pH. That is so because this reaction occurs when CO2 is released:

CO2 + H20 -----> H2CO3 -----> HCO3<sup>-</sup> + H<sup>+</sup>

& more hydrogen ions = a lower (more acidic) pH. So, in active tissues, there are higher levels of CO2, a lower pH, and higher temperatures. In addition, at lower PO2 levels, red blood cells increase production of a substance called 2,3-diphosphoglycerate. These changing conditions (more CO2, lower pH, higher temperature, & more 2,3-diphosphoglycerate) in active tissues cause an alteration in the structure of hemoglobin, which, in turn, causes hemoglobin to give up its oxygen. In other words, in active tissues, more hemoglobin molecules give up their oxygen. Another way of saying this is that the oxygen-hemoglobin dissociation curve 'shifts to the right' (as shown with the light blue curve in the graph below). This means that at a given partial pressure of oxygen, the percent saturation for hemoglobin with be lower. For example, in the graph below, extrapolate up to the 'normal' curve (green curve) from a PO2 of 40, then over, & the hemoglobin saturation is about 75%. Then, extrapolate up to the 'right-shifted' (light blue) curve from a PO2 of 40, then over, & the hemoglobin saturation is about 60%. So, a 'shift to the right' in the oxygen-hemoglobin dissociation curve (shown above) means that more oxygen is being released by hemoglobin - just what's needed by the cells in an active tissue!

Carbon dioxide - transported from the body cells back to the lungs as:

- 1 bicarbonate (HCO3) 60%
  - formed when CO2 (released by cells making ATP) combines with H2O (due to the enzyme in red blood cells called carbonic anhydrase) as shown in the diagram below
- 2 carbaminohemoglobin 30%
  - o formed when CO2 combines with hemoglobin (hemoglobin molecules that have given up their oxygen)
- 3 dissolved in the plasma 10%

### Carbon dioxide transport



### VI. Gas Exchange and Oxygen Transport

A. Partial pressure equals the total pressure times the fractional gas concentration.

**B.** Assuming that total pressure is atmospheric (760 mm Hg) and the fractional concentration of O2 is 0.21, then Po2 = 0.21 × 760 = 160 mm Hg

C. The partial pressure of humidified inspired air is calculated as follows:

PI gas = F gas (Patm - PH2O),

where Patm = atmospheric pressure PI gas = partial pressure of inspired gas PH2O = partial pressure of H2O vapor F gas = concentration of gas The partial pressure of H2O at 37° is 47 mm Hg. Thus,

*Pl*o2 =0.21 (760 - 47) = 150 mm Hg

**D. Because 2% of cardiac output** bypasses the pulmonary circulation via a **physiologic shunt**, the PO2 of arterial blood is lower than that of alveolar air.

**E.** Physically dissolved oxygen (O2) consists of free O2 molecules in solution. O2 is also carried in blood bound to hemoglobin (Hb).

**F. The amount of physically dissolved O2** is directly proportional to the **PO2**. The units of concentration for a dissolved gas are mL gas per 100 mL blood.

**G. At body temperature,** blood equilibrated with a normal PO2 (~ 100 mm Hg) contains only 0.3 mL O2/100 mL blood (0.3 vol%), which is not enough to supply the needs of the tissues.



Partial Pressures of Gases in Inspired Air and Alveolar Air

**H. Saturation is the percentage of Hb**-binding sites occupied by O2.

**1. Each gram of Hb** has an oxygen capacity of 1.34 mL O2, and because 100 mL of blood contains 15 g Hb, completely oxygenated blood contains approximately 20 mL O2 (1.34 mL O2 × 15 g Hb/100 mL).

2. Thus, the oxygen capacity of Hb in blood is approximately 20 mL O2/100 mL of blood or 20 vol%.

**3. Each Hb molecule contains four subunits:** two have  $\alpha$  chains and two have  $\beta$  chains.

I. Physiologic implications of the oxyhemoglobin dissociation curve include the following

1. Hb combines rapidly and reversibly with O2 to form oxyhemoglobin.

**2.** The saturation curve has a sigmoid shape because oxygenation of the first heme group of the Hb molecule increases the affinity of O2 for the other heme group



Figure 3–5. Saturation versus partial pressure. Each saturation curve has a single  $P_{50}$ , which is the  $PO_2$  that gives 50% saturation. Normal  $P_{50}$  = 26 mm Hg.

### Gas Exchange

In a mixture of different gases, each gas contributes to the total pressure of the mixture. The contribution of each gas, called the partial pressure, is equal to the pressure that the gas would have if it were alone in the enclosure. **Dalton's law** states that the sum of the partial pressures of each gas in a mixture is equal to the total pressure of the mixture.

The following factors determine the degree to which a gas will dissolve in a liquid:

- The partial pressure of the gas. According to **Henry's law**, the greater the partial pressure of a gas, the greater the diffusion of the gas into the liquid.
- The solubility of the gas. The ability of a gas to dissolve in a liquid varies with the kind of gas and the liquid.
- The temperature of the liquid. Solubility decreases with increasing temperature.

Gas exchange occurs in the lungs between alveoli and blood plasma and throughout the body between plasma and interstitial fluids. The following factors facilitate diffusion of  $O_2$  and  $CO_2$  at these sites:

- Partial pressures and solubilities. Poor solubility can be offset by a high partial pressure (or vice versa). Compare the following characteristics of O<sub>2</sub> and CO<sub>2</sub>:
  - Oxygen. The partial pressure of  $O_2$  in the lungs is high (air is 21%  $O_2$ ), but is solubility poor.
  - Carbon dioxide. The partial pressure of  $CO_2$  in air is extremely low (air is only 0.04%  $CO_2$ ), but its solubility in plasma is about 24 times that of  $O_2$ .
- Partial pressure gradients. A gradient is a change in some quantity from one region to another. Diffusion of a gas
  into a liquid (or the reverse) occurs down a partial pressure gradient-that is, from a region of higher partial
  pressure to a region of lower partial pressure. For example, the strong partial pressure gradient for O<sub>2</sub> (pO<sub>2</sub>) from
  alveoli to deoxygenated blood (105 mm Hg in alveoli versus 40 mm Hg in blood) facilitates rapid diffusion.
- Surface area for gas exchange. The expansive surface area of the lungs promotes extensive diffusion.

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• Diffusion distance. Thin alveolar and capillary walls increase the rate of diffusion.

### **Gas Transport**

### Oxygen is transported in the blood in two ways:

- A small amount of O<sub>2</sub> (1.5 percent) is carried in the plasma as a dissolved gas.
- Most oxygen (98.5 percent) carried in the blood is bound to the protein hemoglobin in red blood cells. A fully
  saturated oxyhemoglobin (HbO<sub>2</sub>) has four O<sub>2</sub> molecules attached. Without oxygen, the molecule is referred to as
  deoxygemoglobin (Hb).

The ability of hemoglobin to bind to  $O_2$  is influenced by the partial pressure of oxygen. The greater the partial pressure of oxygen in the blood, the more readily oxygen binds to Hb. The oxygen-hemoglobin dissociation curve, shown in Figure 1, shows that as  $pO_2$  increases toward 100 mm Hg, Hb saturation approaches 100%. The following four factors decrease the affinity, or strength of attraction, of Hb for  $O_2$  and result in a shift of the  $O_2$ -Hb dissociation curve to the right:



- Increase in temperature.
- Increase in partial pressure of CO<sub>2</sub> (pCO<sub>2</sub>).
- Increase in acidity (decrease in pH). The decrease in affinity of Hb for O<sub>2</sub>, called the Bohr effect, results when H+ binds to Hb.
- Increase in BPG in red blood cells. BPG (bisphosphoglycerate) is generated in red blood cells when they produce energy from glucose.

Carbon dioxide is transported in the blood in the following ways.

- A small amount of CO<sub>2</sub> (8 percent) is carried in the plasma as a dissolved gas.
- Some CO<sub>2</sub> (25 percent) binds to Hb in red blood cells forming carbaminohemoglobin (HbCO<sub>2</sub>). (The CO<sub>2</sub> binds to a place different from that of O<sub>2</sub>.)
- Most CO<sub>2</sub> (65 percent) is transported as dissolved bicarbonate ions (HCO<sub>3</sub>-) in the plasma. The formation of HCO<sub>3</sub>-, however, occurs in the red blood cells, where the formation of carbonic acid (H<sub>2</sub>CO<sub>3</sub>-) is catalyzed by the enzyme carbonic anhydrase, as follows.

### $CO_2 + H_2O fl \ddagger H_2CO_3 fl \ddagger H^* + HCO_3.$

Following their formation in the red blood cells, most H+ bind to hemoglobin molecules (causing the Bohr effect) while the remaining H+ diffuse back into the plasma, slightly decreasing the pH of the plasma. The  $HCO_{3-}$  ions diffuse back into the plasma as well. To balance the overall increase in negative charges entering the plasma, chloride ions diffuse in the opposite direction, from the plasma to the red blood cells (chloride shift).

### **Control of Respiration**

Respiration is controlled by these areas of the brain that stimulate the contraction of the diaphragm and the intercostal muscles. These areas, collectively called respiratory centers, are summarized here:

- The medullary inspiratory center, located in the medullar oblongata, generates rhythmic nerve impulses that stimulate contraction of the inspiratory muscles (diaphragm and external intercostal muscles). Normally, expiration occurs when these muscles relax, but when breathing is rapid, the inspiratory center facilitates expiration by stimulating the expiratory muscles (internal intercostal muscles and abdominal muscles).
- The pheumotaxic area, located in the pons, inhibits the inspiratory center, limiting the contraction of the inspiratory muscles, and preventing the lungs from overinflating.
- The apneustic area, also located in the pons, stimulates the inspiratory center, prolonging the contraction of inspiratory muscles.

The respiratory centers are influenced by stimuli received from the following three groups of sensory neurons:

- Central chemoreceptors (nerves of the central nervous system), located in the medulla oblongata, monitor the chemistry of cerebrospinal fluid. When CO<sub>2</sub> from the plasma enters the cerebrospinal fluid, it forms HCO<sub>3</sub>- and H+, and the pH of the fluid drops (becomes more acidic). In response to the decrease in pH, the central chemoreceptors stimulate the respiratory center to increase the inspiratory rate.
- Peripheral chemoreceptors (nerves of the peripheral nervous system), located in aortic bodies in the wall of the aortic arch and in carotid bodies in the walls of the carotid arteries, monitor the chemistry of the blood. An increase in pH or pCO<sub>2</sub>, or decrease in pO<sub>2</sub>, causes these receptors to stimulate the respiratory center.
  - Stretch receptors in the walls of bronchi and bronchioles are activated when the lungs expand to their physical limit. These receptors signal the respiratory center to discontinue stimulation of the inspiratory muscles, allowing expiration to begin. This response is called the inflation (Hering-Breur) reflex.

### Cliff notes

**3.** The **O2 capacity** is the maximum amount of O2 that can be bound to Hb and is determined by the Hb concentration in blood.

4. The O2 content is the total amount of O2 carried in the blood whether bound or dissolved in solution.

**5.** Figure 3–6 shows the **dissociation curve** as a function of partial pressure for two different amounts of Hb. The Hb concentration in normal blood is about 15 g/100 mL. The maximal amount of O2/100 mL (98% saturation) in combination with Hb is 20.1 mL O2/100 mL (1.34 mL × 15). The amount of dissolved O2 is a linear function of the PO2 (0.003 mL/100 mL blood/mm Hg PO2).

**a.** In curve A, the total amount of O2 bound to Hb at 98% saturation is 19.7 mL O2/100 mL blood. With the 0.3 mL/100 mL of dissolved O2 added, the total O2 content is approximately 20 mL O2/100 mL of blood.

**b.** In curve **B**, the Hb is also 98% saturated, but this blood contains only 7.5 g Hb/100 mL blood. The total amount of O2 bound to Hb is only 10 mL O2/100 mL blood. Because of the lower amount of Hb, the amount of O2 is about half that of normal blood.

J. Several factors influence the oxyhemoglobin dissociation curve

**1. Shifts to the right** occur when the affinity of Hb-binding sites for O2 is decreased and it is easier for tissues to extract oxygen.

a. Causes of this shift include increased CO2 (Bohr effect), increased H+ (decreased pH), increased temperature, and increased 2,3-diphosphoglycerate (2,3-DPG).

b. Anemia is characterized by a reduced Hb concentration in blood and decreased arterial oxygen content.



**Figure 3–6.** O<sub>2</sub> content versus partial pressure for two different hemoglobin (Hb) concentrations. Curve A represents normal Hb levels in blood (15 g/100 mL). Curve B represents a reduced concentration of Hb in blood (7.5 g/100 mL). The main effect of the lower Hb concentration is a reduced carrying capacity of the blood. Thus, in curve B, the total amount of O<sub>2</sub>/100 mL of blood is around 10 mL O<sub>2</sub>/100 mL, instead of the normal 20 mL O<sub>2</sub>/100 mL.



Figure 3-7. Changes in affinity of hemoglobin (Hb) for  $O_2$  (oxyhemoglobin dissociation curve).

2. Shifts to the left occur when there is increased affinity of Hb for O2 and it is

more difficult for tissues to extract oxygen.

a. Causes of this shift include decreased temperature, decreased PCO2, decreased H+ (increased pH), and decreased 2,3-DPG.

### b. Stored blood loses 2,3-DPG and fetal Hb, and both decreases shift the curve to the left.

**c. Polycythemia** (increased number of red blood cells in blood) is characterized by a higher than normal concentration of Hb in the blood, a shift to the left in the oxyhemoglobin dissociation curve, and increased arterial oxygen content.

**VII. Carbon Dioxide Transport** 

A. CO2 is an important end product of aerobic cellular metabolism and is, therefore, continuously produced by body tissues.

**B.** After formation, CO2 diffuses into the venous plasma, where it is 24 times more soluble than O2 and then passes immediately into red blood cells.

C. CO2 is carried in the plasma in three forms:

**1. Five percent is dissolved CO2**, which is free in solution.

2. Five percent is in the form of carbaminohemoglobin, which is CO2 bound to hemoglobin.

**3. Ninety percent is in the form of bicarbonate** from reaction with H2O to form carbonic acid in the red blood cells, which dissociates into hydrogen and bicarbonate.

**D**. Bicarbonate leaves the red blood cells in exchange for chloride (called a **chloride shift**) to maintain electrical neutrality and is transported to the lungs

**E.** Inside the red blood cell, deoxyhemoglobin is a better buffer for H+, and H+ binding by deoxygenated Hb occurs in peripheral tissues where CO2 is high.

**F. The enhancement of CO2** binding to deoxygenated Hb at the venous end of capillaries leads to the formation of bicarbonate in red blood cells.

G. In the lung, the reaction in the pulmonary capillaries is in the opposite direction:

- O2 is taken up by the red blood cells, CO2 is released to the alveolus for expiration, and HCO3
- enters the red blood cells in exchange for CI- and combines with H+ to form H2CO3.

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H. In summary, CO2 entering the red blood cells causes a decreased pH that facilitates O2 release. In lungs, O2 binding to Hb lowers the CO2 capacity of blood by lowering the amount of H+ bound to Hb.

**VIII. Respiration Control** 

A. For spontaneous breathing, respiratory muscle activity depends on neural input.

### 1. Two main groups of respiratory neurons,

the dorsal respiratory group and the ventral respiratory group,

are found in the medulla.

### 2. These groups comprise the medullary respiratory center.

**a.** The **dorsal respiratory group** is responsible for the inspiratory respiratory rhythm; input comes from the vagus and glossopharyngeal nerves and output is via the phrenic nerve to the diaphragm.

**b.** The **ventral respiratory group** innervates both inspiratory and expiratory muscles but is primarily responsible for expiration. It becomes active only during exercise.

**B.** The **apneustic center** in the lower pons has an intrinsic rhythm and when stimulated promotes prolonged inspirations.

C. Apneustic breathing is an abnormal breathing pattern characterized by prolonged





Figure 3-8. Chloride shift.



Figure 3-9. Neural control of respiration.

D. The pneumotaxic center is located in the upper pons and has an inhibitory influence on the apneustic center. If the connection between the pneumotaxic center and apneustic center is cut, apneustic breathing occurs.



E. <u>Central chemoreceptors</u> are located in the ventrolateral medulla and are the **most important chemoreceptors in** the regulation of normal breathing.

The receptors are stimulated by cerebrospinal fluid (CSF) [H+] and CO2 because they are sensitive to CSF pH.
 Because the blood-brain barrier is permeable to CO2, increases in PCO2 and [H+] stimulate breathing and decreases in PCO2 and [H+] inhibit breathing.

3. Therefore, the primary drive for ventilation is CO2 (H+) on the central chemoreceptors.

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**F. Peripheral chemoreceptors** are found in small bodies in two locations.

Carotid bodies (the more important of the two types) are found at the bifurcation of the common carotid arteries (ie, near the carotid sinus). Aortic bodies are found near the aortic arch.
 These bodies have two different receptors:

a. H+/CO2 receptors monitor arterial PCO2, and increased PCO2 stimulates ventilation.

b. PO2 receptors monitor dissolved O2, and decreased arterial PO2 (> 60 mm Hg) stimulates breathing.

### **Brain Stem Respiratory Centres**

Three areas within the Pons (two centres) and the medulla oblongata (one centre) control autonomic breathing.

Rhythmicity Centre 1 Situated in the Medulla oblongata

- 2 **I neurons** stimulate spinal motor neurons that innervate the respiratory muscles producing **Inspiration**
- 3 **E neurons** inhibit the I neurons and thus produce expiration by relaxation of the respiratory muscles
- 4 I and E neuronal activity varies in a reciprocal way

so that a rhythmic pattern is obtained

Apneustic Centre	1	Situated in the Pons	
	2	Stimulate the I neurons in the Medulla Oblongata	
	3	Result in Inspiration	
	4	Provides a constant stimulus for inspiration	
Pneumotaxic Centre	1	Situated in the Pons	
	2	Seems to antagonise the apneustic centre	
	3	Inhibits inspiration	

### **CONTROL OF RESPIRATION**

OVERVIEW OF RESPIRATORY CONTROL

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The respiratory system has no intrinsic driving system like the heart. It is therefore absolutely dependent on an external neural drive.

Like all other control systems, the respiratory system has three parts.



*Figure 1.* Block diagram showing major components of ventilatory control. Inspiratory neurons are facilitated by the reticular activating system and chemoreceptor output but inhibited by expiratory neurons throughout expiration and off-switch neurons late in inspiration. These off-switch neurons are facilitated by the pneumotaxic center and the vagal stretch receptor input. Note that the effects of the central and peripheral chemoreceptors are multiplicative (x), not additive.

Sensors and their afferents: Providing information on what the system is doing.

Central Controller: Compares intended operation with how the sensors say the system is actually working.

Efferents and Effectors: The respiratory muscles which actually carry out respiration.

Main goals of the respiratory control system

An alveolar ventilation sufficient to maintain normal blood gases.

Changes in alveolar ventilation rate sufficient to adapt to changing environments or metabolic needs (eg. exercise).

Adaptability to allow other activities such as talking or eating which share anatomical structures with the lung.

### CHEMICAL CONTROL OF RESPIRATION

Two sets of chemoreceptors exist

 $\label{eq:contract} \mbox{Central Chemoreceptors: Responsive to arterial $P_{CO_2}$ by way of hydrogen ion concentration in cerebrospinal fluid (CSF).}$ 

Peripheral Chemoreceptors: Responsive to arterial  $P_{\rm O_2}$  ,  $P_{\rm CO_2}$  and hydrogen ion concentration.

The most important single driver of ventilation is  $P_{a_{CO_2}}$  acting on the central chemoreceptors by altering CSF [H<sup>+</sup>]. Advantages of a

 $P_{a_{CO_2}}$  based control system are:

CO<sub>2</sub> production is related to oxygen consumption.

CO<sub>2</sub> production is related to pH.

 $P_{\rm CO_2}$  is linearly related to content over the physiological range.

Central chemoreceptors increase ventilation in response to increased  $\,P_{\!A_{COD}}^{}$  .



*Figure 2.* Central chemoreceptor area on the ventral surface of the medulla. Rostral (RA) and caudal (CA) areas (hatched) are sensitive to CO<sub>2</sub> tension and hydrogen ion, whereas the intermediate area (IA) appears to relay chemoreceptor signals. (Roman numerals indicate nerves.) (Redrawn from Loeschcke, H.H.: Central chemoreceptors. In Pallot, D.J. (ed.): *Control of Respiration*. New York: Oxford University Press, 1983, p. 57.)

Central chemosensitive cells are located on the ventral surface of medulla.

Chemosensitive cells are bathed in CSF which has a  $\,P_{CO_2}\,$  equilibrium with arterial  $\,P_{CO_2}\,$  .

CSF carbon dioxide combines with water to form carbonic acid which dissociates to form hydrogen ions and bicarbonate.

The CSF hydrogen ions diffuse into the tissue to stimulate medullary chemoreceptors.

Increased arterial H<sup>+</sup> may also stimulate central chemoreceptors slightly, but it does not diffuse into CSF as easily as CO<sub>2</sub>. Its effect is likely due mainly to increasing cerebral blood flow in the chemoreceptor region.

Chronic Adaptation of Central Chemoreceptors. Transport of  $HCO_{3^{-}}$  ions across the blood brain barrier buffers CSF hydrogen ion changes. This occurs in hours to days.

 $P_{a_{CO_{2}}}$  enters CSF during hypercapnia.

 $P_{a_{CO_2}}$  leaves CSF during hypocapnia.

 $\overline{P_{a_{\rm CO_2}}}$  is exchanged for Cl via a specific anion carrier.

Chronic CO<sub>2</sub> retention.  $P_{a_{CO_2}}$  movement into CSF is responsible for the decreased ventilatory drive via central chemoreceptors in chronic CO<sub>2</sub> retention of obstructive disease. The only remaining drive to breath is stimulation of peripheral chemoreceptors by low  $P_{O_2}$ .

Peripheral chemoreceptors increase ventilation in response to decreased  $P_{a_{\Omega_{\alpha}}}$  .

Location: Carotid bodies at bifurcation of common carotid. Aortic bodies found between ascending aorta and pulmonary artery.

Carotid bodies are sensitive to  $P_{a_{\Omega_2}}$ ,  $P_{a_{\Omega_2}}$ , and pH. Afferents in glossopharyngeal nerve.

Aortic bodies are sensitive to  $\,P_{a_{O_2}}\,$  and  $\,P_{a_{CO_2}}$  , but not pH. Afferents in vagus nerve.

#### **Carotid Body Function**

Carotid bodies have one of the highest flows per unit weight in body. (2 L/min/100 g)

Carotid body oxygen consumption is (8 ml O<sub>2</sub>/min/100g). This is above average for the body, but low in proportion to carotid body flow. Therefore, carotid bodies have a tiny arterial-venous O<sub>2</sub> difference, and the receptor cells are exposed mainly to arterial  $P_{O_2}$  levels.

Neural impulses from the carotid body increase as  $P_{a_{O_2}}$  falls below about 60 mmHg. This responsiveness is potentiated by acidosis and hypercapnia. The responsiveness is blunted by alkalosis and hypocapnia.



*Figure* 3. Carotid body nerve activity (per cent of maximal) as a function of  $P_aO_2$ . The enhanced response to hypoxia as arterial pH decreases from 7.5 to 7.2 and PCO<sub>2</sub> increases from 25 to 60 is shown. (Redrawn from Hornbein, T.P.: The relation between stimulus to chemoreceptors and their response. In: Torrance, R.W. (ed.): *The Proceedings of the Wates Foundation Symposium on Arterial Chemoreceptors*. Oxford: Blackwell, 1968, pp. 65-76.)

#### **Aortic Body Function**

Respond more weakly than carotid bodies  $P_{a_{O_2}}$  decreases. Also less sensitive to  $P_{a_{CO_2}}$  changes.

The aortic bodies seem to respond somewhat to changes in oxygen content such as are seen in anemia. This is due to the fact that the arterial-venous oxygen difference is greater for these cells than for the carotid bodies. Thus, the receptor cells see a lower average oxygen when content is reduced.

Summary of Ventilatory Response to  $\ P_{a_{CO_2}} \$  and pH



*Figure 4.* Stimulation of alveolar ventilation by decreased arterial pH or increased P<sub>a</sub>CO<sub>2</sub>. (Redrawn from Guyton, A.C.: *Textbook of Medical Physiology.* 4<sup>th</sup> ed. Philadelphia: W.B. Saunders, 1971, p. 500.)



*Figure 5.* Ventilatory response to changes in  $P_ACO_2$  at various fixed  $P_AO_2$  values. The slopes progressively increased as  $P_AO_2$  was decreased, but the slope of the curve as unchanged when  $P_AO_2$  exceeded 110 mmHg. (Redrawn from Nielson, M., and Smith, H.: Studies on the regulation of respiration in acute hypoxia with an appendix on respiratory control during prolonged hypoxia. *Acta. Physiol. Scand.* 24:293-313, 1952.)

Increase CSF hydrogen ion concentration (decreased pH) leads to increased ventilation. Such an increase in CSF [H<sup>+</sup>] is mainly secondary to a  $P_{a_{COD}}$  increase.

Metabolic acidosis decreases arterial pH. The pH stimulates peripheral chemoreceptors to stimulate ventilation. This in turn reduces  $P_{a_{CO_2}}$  and CSF  $P_{CO_2}$ . The reduced  $P_{CO_2}$  reduces CSF [H<sup>+</sup>] and blunts the central drive to breath.

The overall response to pH changes is less than the overall response to  $\,P_{CO_{\gamma}}\,$  changes.

Hypoxia potentiates the ventilatory response to an increase in  $P_{A_{CO_2}}$ . Increased ventilation represents the integrated

response of central and peripheral chemoreceptor stimulation. As  $P_{a_{\Omega_2}}$  falls ventilation is greater at any given

 $P_{a_{CO_2}}$  and rises more rapidly with any increase in  $\ P_{a_{CO_2}}$  .

### OTHER PULMONARY RECEPTORS

Hering-Breuer Reflex. Slowly adapting stretch receptors (SARs) in bronchial airways send afferent information to respiratory centers through vagus.

Stimulation of SARs helps terminate inspiration. This is the Hering-Breuer Response. By affecting the timing of inspiratory termination they affect respiratory frequency.
Stronger sustained stimulation of SARs causes activation of expiratory neurons as well.
At normal tidal volumes in adults these receptors don't appear to be activated at end inspiration and are probably not important. They may help terminate inspiration in infants.
Hering-Breuer reflex is important in adults during moderate and strenuous exercise when tidal volume is increased.
Chronic lung diseases which increase lung compliance augment distension and influence ventilation by stimulating these receptors.
Rapidly adapting stretch receptors (irritant receptors). Respond to mechanical and chemical irritation. These are the receptors involved in reflexes causing coughing, sneezing, bronchoconstriction, and increased airway secretions. Mainly located in epithelium of carinal region.
J-Receptor Reflexes. (Juxtapulmonary Receptors). Respond to increased interstitial volume.
Thought to mediate the hyperpnea associated with increases in left atrial pressure as in vascular congestion and pulmonary edema of other causes.
May mediate apnea of pulmonary embolism when arterial end of capillary is blocked.
Peripheral receptors. Stimulation causes increased inspiration.
Pain receptors in muscles and skin.
Proprioceptors in muscles tendons and joints.
Muscle spindles of diaphragm and intercostal muscles.
Cortical override. We can override the involuntary system on a short term basis for such activities as speaking. This override can not continue indefinitely because the involuntary system eventually asserts itself.
BRAINSTEM SECTION WITH AND WITHOUT VAGAL AFFERENT FEEDBACK
VAGI INTACT VAGI CUT
PREUMOTAXIC CENTER 8

Figure 6

APNEUSTIC CENTER

MEDULLARY CENTER

> SPINAL CORD

+ NEDULLA +

Section above the pons causes no significant alteration of normal respiratory rhythm. Vagotomy removes afferent input from stretch receptors. Inspiration is enhanced because the Hering-Breuer Response is abolished.

Section at midpontine level increases the depth of breathing because signals from the pneumotaxic center in upper pons normally terminate inspiration. When vagotomy is added, apneuses (sustained inspiratory effort) results. Both central and peripheral inhibition of inspiration have been eliminated.

Section between medulla and pons. Respiration is rhythmic if somewhat irregular. Vagotomy has little effect. This shows that basic



Figure 7. Dorsal view of the brainstem showing the major groups of respiratory-related neurons. IV refers to the fourth ventricle. Inspiratory and expiratory neurons are shown by open and hatched regions, respectively.



*Figure 8.* Dorsal view of the brainstem showing facilitory and inhibitory inputs to the nucleus tractus solitarius (NTS) and outflow pathways to inspiratory and expiratory muscle groups. Structures shown include the nucleus parabrachialis medialis (NPSM), nucleus ambiguus (NA), nucleus para-ambigualis (NPA), nucleus retro-ambigualis (NRA), and Botzinger's complex (Bot.)

### Areas involved

Pontine Areas: Pneumotaxic Center; apneustic center.

	Medullary Areas: Ventral Respiratory Group; Dorsal Respiratory Group.
Pneu	umotaxic Center: Act as "off-switch" neurons for inspiration. Stimulation of this area causes earlier termination of inspiration. This in turn causes higher respiratory frequency and reduced tidal volumes.
Apne	eustic Center. Anatomically this area is poorly defined. Stimulation causes apneuses. This area is thought to be an area where inspiratory cutoff information from the pneumotaxic center and vagus are integrated before projecting caudally to the dorsal respiratory group (DRG).
Dors	al Respiratory Group (DRG). Located in NTS. The "upper motor neurons" of inspiration. They also drive ventral respiratory group. Input from virtually all peripheral afferents impinge on the DRG.
Vent	tral Respiratory Group (VRG). Contains both inspiratory and expiratory neurons.
	Inspiratory neurons mainly project to accessory muscles of inspiration and external intercostal.
	Expiratory neurons project to internal intercostals and abdominal muscles. These neurons are quiescent during normal breathing but may become active during exercise.

### **IX. Pulmonary Blood Flow**

### A. Pressures Within the Pulmonary Circuit

**1.** The **most important difference** between the pulmonary and systemic circulations **is the low blood pressure** in the pulmonary arteries. The pulmonary arterial systolic pressure is approximately 22 mm Hg, whereas the left ventricular systolic pressure is around 120 mm Hg.

40 **2. The pulmonary circulation** is a low-resistance circuit that must accommodate the entire cardiac output at rest and during exercise.

3. When pulmonary arterial pressure increases, vascular resistance decreases for two reasons:

a. Increased pressure increases the caliber (distention) of the arteries.

b. Increased pressure causes more capillaries to open (recruitment).

### **B. Effects of Gravity on Blood Flow**

1. Because of the low blood pressures in the pulmonary circulation, gravity has

a large effect on blood flow to different parts of the lung

a. In an upright subject, the effect of gravity causes blood flow to be larger at the base than at the apex. Ventilation is also larger at the base than at the apex.  $V_{A}$ 

b. Although the base receives the greatest ventilation, it does not match the	Q	very high blood flow. Thus, the
base is an underventilated region, in which the ratio is less than 0.8.		

c. Even though the apex receives the lowest ventilation, it is too high for the low blood flow. Therefore, the apex can be

considered an overventilated region, in which the  $\vec{Q}$  ratio is greater than 0.8.

d. An overventilated lung unit acts like dead space, whereas an underventilated lung unit acts like a pulmonary shunt.

2. Regional blood flow in the lungs has been separated into three zones

### **C. Hypoxic Vasoconstriction**

**1. A decrease in alveolar PO2 produces a local vasoconstriction of pulmonary arterioles,** thereby lowering blood flow to that part of the lung.

2. In other systemic organs, hypoxia results in vasodilation of arterioles.

### **D. Pulmonary Edema**

**1.** For normal respiratory function, it is crucial that the alveoli do not accumulate fluid.

**2.** A small amount of fluid moves into peribronchial and perivascular spaces each day but is removed by lymphatic vessels.

**3.** If net fluid movement out of the pulmonary capillaries exceeds the ability of the lymphatic system to remove it, a net fluid accumulation, or edema, occurs.

4. Severe alveolar edema occurs when accumulated fluid in alveoli impairs normal gas exchange.

### 5. The two causes of pulmonary edema are

a. Increased capillary permeability

b. Increased pulmonary blood pressure due to hypoxic vasoconstriction, left heart failure, or loss of surfactant

### **E. Shunts**

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1. In an absolute right-to-left shunt, venous blood is delivered to the left side of the heart without contacting ventilated alveoli; this shunt produces hypoxemia

## a. The shunt results in a decrease in arterial PO2 and widening of the PO2 systemic alveolar-arterial (A-a) difference.

**b.** With a significant pulmonary shunt (such as occurs in regional atelectasis), breathing 100% O2 does not result in a significant increase in systemic arterial PO2, leading to a diagnosis of a pulmonary right-to-left shunt.

**c.** Thus, **overventilating** part of the lung does not compensate for the shunt because the empty Hb-binding sites in the shunted blood will bind the dissolved O2 from the ventilated part of the lung, only slightly increasing PO2 levels.

d. A **physiologic shunt** is the amount of absolute shunt that would cause the observed A-a difference.

2. In a left-to-right shunt, the pressures are higher in the left side of the heart; therefore, hypoxemia is absent. This type of shunt can be due to arterial or ventricular septal defects or patent ductus arteriosis

X. Ventilation-Perfusion Differences (Figure 3–12)

A. The relative difference between alveolar ventilation (VA) and blood flow (Q) is known as the ratio. B. Thus, the local alveolar gas composition is not determined by ventilation alone or by blood flow (ie, perfusion) alone

but by the ratio between ventilation and perfusion. In the normal lung, the

ratio is approximately 0.8.

 $V_{\rm A}$ 

**C. Physiologic dead space** is defined as anatomic dead space plus the volume of all airways that behave as if they have received no blood flow.

1. In health, anatomic dead space and physiologic dead space are essentially equal.

2. In ventilation-perfusion mismatch, the amount of physiologic dead space is much greater than the amount of anatomic dead space.

a. Some regions of the lung may have a high

, and PO2 in these alveoli is below average.

 $V_{\rm A}$ 

**b.** The **Bohr method** measures the volume of all airways in which no CO2 has been added from the blood; this is the physiologic dead space.



## Figure 3-12. Ventilation-perfusion difference.

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c. In many pulmonary diseases, the physiologic shunt and the physiologic dead space will be increased.

d. The consequence of increased physiologic dead space is wasted ventilation.

**D.** Hypoventilation is associated with equal decreases in PO2 in the alveolar, pulmonary end capillary, and systemic arterial compartments. Supplemental oxygen or increased alveolar ventilation will return arterial PO2 to normal.

E. Diffusion impairment refers to a lung structural problem (eg, increased thickness of lung membrane).

1. With significant diffusion impairment, the A-a gradient widens.

2. Supplemental oxygen will increase the gradient across the alveolar membranes and return arterial PO2 toward normal.

**F. Exercise** increases ventilation and pulmonary blood flow. During exercise, the alveolar  $\dot{Q}$ 0.8, ventilation increases more than cardiac output, and base-to-apex flows become more equal.

ratio is greater than

### XI. Special Environments A. High Altitude

**1. At high altitude,** atmospheric pressure is reduced from 760 mm Hg, **resulting in** decreased alveolar and arterial PO2 (**hypoxemia**).

**2.** Low PO2 stimulates peripheral chemoreceptors, inducing hyperventilation, a decrease in alveolar and arterial PCO2, and respiratory alkalosis.

**3. Hypoxemia stimulates erythropoietin**, a hormone produced by the kidney that increases red blood cell production and **can lead to polycythemia**.

The increased Hb production increases O2 content of the blood.

**4.** 2,3-DPG levels increase, shifting the oxyhemoglobin dissociation curve to the right and facilitating O2 extraction by the tissues.

**5.** Hypoxemia also **results in hypoxic vasoconstriction** (ie, pulmonary vasoconstriction), resulting eventually in hypertrophy of the right ventricle due to increased work of the right heart.

### **B. Hyperbaric Chamber**

**1.** Breathing room air (21% O2; 79% N2) in a hyperbaric environment increases the partial pressure of O2 and N2 in alveoli and arterial blood. Elevated PO2 can produce oxygen toxicity, and the high PN2 can lead to the **bends** (also known as caisson disease).

**2.** Sudden decompression causes bubbles of nitrogen to accumulate in the blood and tissues. Treatment is recompression and gradual decompression.

References : Road map physiology for the USMLE