

# Chapter 2

## Respiratory Physiology

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**Keywords** Respiratory system • Ventilation • Inspiration • Expiration • Pleural and transmural pressure • Lung volumes •  $FEV_1$  • FRC • Functional residual capacity • Hysteresis • Diffusing • Diffusing capacity • Miget diagrams • Hypoxic pulmonary vasoconstriction

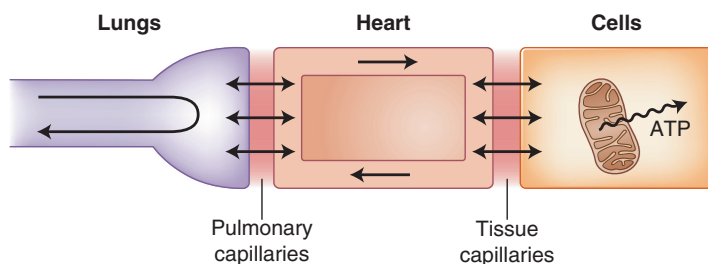
### Introduction

The primary function of the respiratory system is to exchange carbon dioxide and oxygen in order to support metabolism. The respiratory system accomplishes this by bringing blood and air in close proximity across a large, diffusive surface area. Two bulk flow pumps, the heart and lungs move blood and gas, respectively. Two diffusion systems allow exchange of blood and gas between the lungs and pulmonary capillaries, and then tissue capillaries and cells (Fig 2-1).

### Ventilation

#### Components of the Lung

The respiratory system is made of two components, the lung and chest wall. Functionally, the lung is divided into two regions: a conducting zone comprised of airways larger than respiratory



**Figure 2-1** – Weibel diagram.

bronchioles, and a respiratory zone containing smaller airways with gas exchanging units called alveoli. The chest wall includes the rib cage, abdomen, and diaphragm. A continuous envelope of parietal and visceral pleura separates the chest wall from the lung with a potential pleural space between.

## Inspiration and Expiration

The diaphragm is the primary muscle of inspiration. It is a dome-shaped structure that forces abdominal contents downward and forward with contraction resulting in an increase in volume of the thorax. Contraction of external intercostal muscles between adjacent ribs also aids in increasing the thoracic volume.

Expiration is passive during quiet breathing and *always passive* during mechanical ventilation in relaxed or anesthetized patients. During expiration the respiratory system returns toward its resting volume as determined by the intrinsic elastic properties of the lung and chest wall. When ventilation is increased, expiration becomes active and the muscles of the abdominal wall and internal intercostals contract with a resultant decrease in the diameter and volume of the thorax.

A number of accessory muscles contribute to ventilation when the respiratory system is taxed. These include the sternocleidomastoids, pectoralis, trapezius, and muscles of the vertebral column.

## Pleural and Transmural Pressure

The pressure inbetween the visceral and parietal pleura of the lung (pleural pressure) is transmitted to regions continuous with the pleural space including the pericardium and great vessels. As a result pleural pressure significantly influences cardiac physiology.

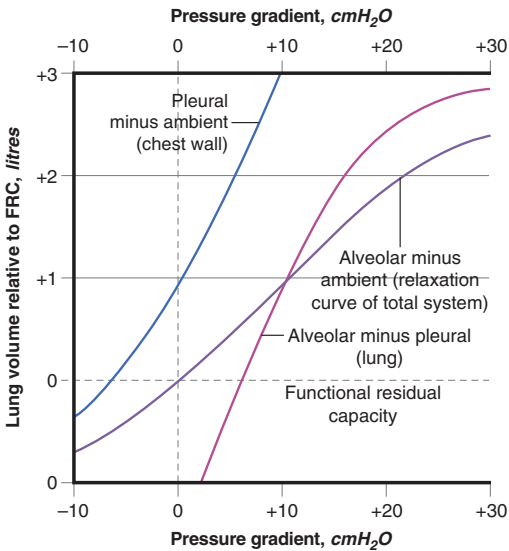
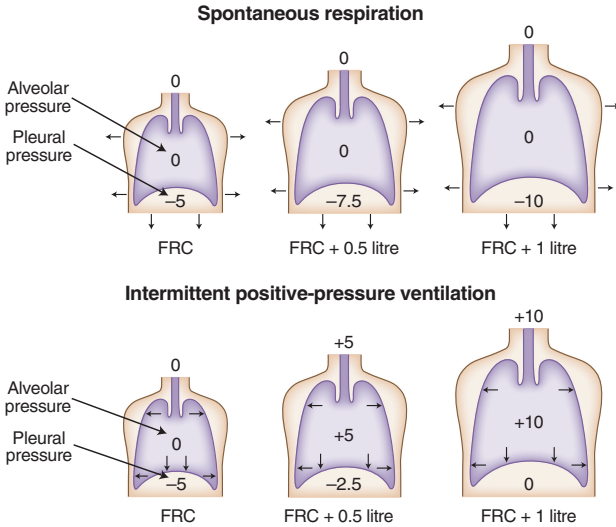
The transmural pressure across the lung parenchyma is alveolar pressure, the pressure inside the lung, minus pleural pressure. As seen in Fig 2-2, the change in pleural pressure required for a given volume change during spontaneous ventilation is dominated by the mechanical properties of the lung and is negative during inspiration. During mechanical ventilation the change in pleural pressure required for a given volume change is dominated by chest wall mechanical properties and is positive during lung inflation. However, unlike pleural pressure, the change in transmural pressure across the lung parenchyma required for a given volume change is the same during both spontaneous and mechanical ventilation (see graph in Fig 2-2).

## Control of Breathing

Details regarding the control of respiration remain topics of controversy. It is thought that an intrinsic respiratory rhythm is generated in the central nervous system (CNS), analogous to cardiac pacemakers. Rate and depth of breathing are altered by  $\text{PaCO}_2$ ,  $\text{PaO}_2$ , and pH.

$\text{PaCO}_2$  is normally the dominant factor governing moment-to-moment respiration. Changes in  $\text{PaCO}_2$  from a set point result in increased or decreased respiratory drive.  $\text{CO}_2$  diffuses freely across the blood brain barrier resulting in similar changes in cerebro-spinal fluid (CSF)  $\text{PaCO}_2$ ,  $\text{HCO}_3^-$ , and  $\text{H}^+$ . *Central* chemo-receptors in the pons and medulla respond to changes in CSF  $\text{PaCO}_2$  and hydrogen ion concentration.

$\text{PaO}_2$  modulates respiration through *peripheral* chemoreceptors (principally carotid and aortic bodies). Some patients exhibit complete loss of hypoxic respiratory drive following bilateral carotid



**Figure 2-2** – Diagram showing different pleural pressures with mechanical and spontaneous ventilation and diagram of lung volume vs. transmural pressure.

body resection. Peripheral chemoreceptors also respond to  $\text{PaCO}_2$ , but this is less important than the central response to  $\text{PaCO}_2$ . Carotid, but not aortic bodies respond to changes in pH.

Ventilation may additionally be influenced by other peripheral chemoreceptors, pulmonary stretch receptors, juxta-capillary receptors, pain, temperature, blood pressure, conscious volition, and other inputs. The integration of these factors is complex and poorly understood. At normal  $\text{PaCO}_2$ , hypoxia must be severe (50 mmHg) to drive respiration, whereas minor fluxes in  $\text{PaCO}_2$  prompt compensatory ventilatory changes, defending  $\text{PaCO}_2$  within a tight range. However, the  $\text{CO}_2$  ventilatory response curve is left-shifted and steeper at decreased  $\text{PaO}_2$ .

In some disease states, notably COPD, the sensitivity to increased  $\text{PaCO}_2$  is diminished. Such patients are frequently labeled as dependent on hypoxic drive, and supplemental oxygen is withheld for fear of depressing ventilation. Evidence exists that such patients exhibit near baseline minute ventilation despite increased  $\text{FiO}_2$ , and that the observed increase in  $\text{PaCO}_2$  is due to disruption of  $\dot{V}/\dot{Q}$  matching (increased dead space due to inhibition of hypoxic pulmonary vasoconstriction (HPV)), rather than hypoventilation (1, 2). The clinical pearl is that if a COPD patient is hypoventilating following surgery, withdrawal of supplemental oxygen is *not* the solution. Other causes should be sought (narcotics, pain, residual volatile agent, residual paralytic, obstruction, etc.).

## Lung Volumes

The following static lung volumes are conventionally defined. A capacity is the sum of two volumes.

- *Residual volume* (RV) is the volume of gas remaining in the lungs after a maximal expiration. It is approximately 1.2 l in a 70-kg human.
- *Tidal volume* (Vt) is the volume of gas exhaled from inspiration to expiration. Vt can also be measured during inhalation. It is approximately 0.5 l in a 70-kg human.

- *Total lung capacity* (TLC) is the volume of gas in the lungs following a maximal inspiration (Vital capacity + RV). It is approximately 6.0 l in a 70-kg human.
- *Vital capacity* (VC) is the volume of gas exhaled from a maximal inspiration to maximal expiration (TLC - RV). It is approximately 4.6 l in a 70 kg human. TLC and RV are set by the mechanical properties of the respiratory system.

### FEV<sub>1</sub> and FVC

Two particularly useful pulmonary function tests are the forced volume of gas exhaled in one second (FEV<sub>1</sub>) and the forced vital capacity (FVC). In health, FEV<sub>1</sub> is approximately 80% of FVC. In restrictive lung diseases both FEV<sub>1</sub> and FVC are reduced but the ratio of FEV<sub>1</sub>/FVC is normal. In obstructive diseases FEV<sub>1</sub> is disproportionately reduced compared to FVC. In addition, the flow volume loop is typically concave toward the volume axis in obstructive, but not restrictive disease. All lung volumes and flows should always be examined as a percentage of predicted values based on height, age, sex, and ethnicity.

### Compliance, Elastance

*Compliance* is volume change as a function of transmural pressure change, or the slope of a volume pressure curve. *Elastance* is the reciprocal of compliance. Elastic recoil is the transmural pressure at a specific volume.

Each of these quantities may be measured for the lung or chest wall alone, or for the sum of the respiratory system. They are static properties and are measured with the respiratory muscles relaxed, with no gas flow and an open airway.

### Relaxation Volume and Functional Residual Capacity

The volume of a structure when its transmural pressure is zero is its *relaxation volume*. When the transmural pressure across an

isolated relaxed chest wall is zero it contains approximately 75% of its TLC volume, whereas the isolated lung contains a volume slightly below RV when its transmural pressure is zero. The volume at which the elastic recoil of the lung and chest wall are equal, and opposite is the relaxation volume of the respiratory system.

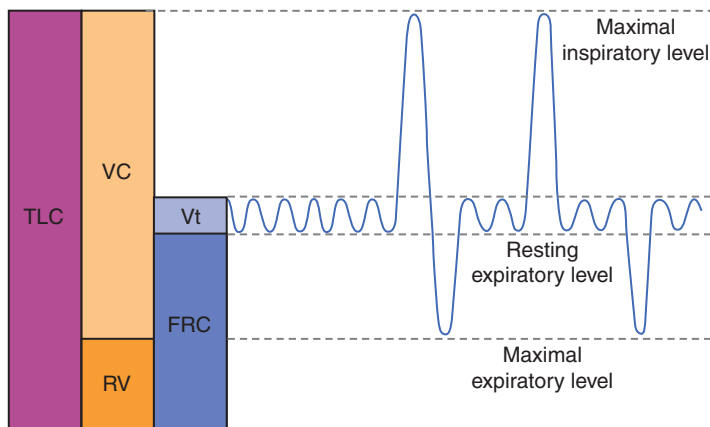
*Functional Residual Capacity* (FRC) is the volume of gas in the lung at end expiration. It should be distinguished from the relaxation volume defined above. In healthy adults at rest FRC is essentially equal to the relaxation volume of the respiratory system, and FRC is usually treated as synonymous with relaxation volume. This is a source of confusion as the two volumes can be different. FRC is variously used to refer to:

1. Relaxation volume of the respiratory system
2. The volume of gas in the lung at the end of a “normal” expiration
3. The volume of gas in the lung at the end of any expiration

The reader is often required to decide which meaning was intended by context. In many situations these volumes are different. For example, the neonatal chest wall is much more compliant than in adults; while this may facilitate passage through the birth canal, it lowers the relaxation volume of the respiratory system. To prevent closing of airways that would occur if FRC were to drop to relaxation volume, neonates end expiration by closing the glottis. Another example where FRC and relaxation volume may differ is in obstructive lung disease where FRC is dynamically determined and may be considerably above relaxation volume.

Although the elastic properties and relaxation volumes of the lung and chest wall are different, the compliances or slopes of the curve of the two structures are very similar throughout the midlung volumes. The compliance of the chest wall falls at low lung volumes, and the compliance of the lung falls at high lung volumes. See Fig 2-2.

FRC and relaxation volume are affected by body size, sex, age, diaphragmatic muscle tone, posture, anesthesia, and various pathologic states that affect the lung, chest wall, or muscle tone.



**Figure 2-3** – Lung volumes.

FRC is measured using either a nitrogen washout technique, the wash-in of a tracer gas, or whole body plethysmography.

*The clinical significance of FRC* is twofold. First, it represents a reservoir of gas which may provide oxygen to the circulation during periods of apnea (e.g., during intubation). Second, maintaining an adequate lung volume at end expiration is critical to keeping airways open. If airways close during expiration and do not open on a subsequent inspiration, alveoli distal to the closure will undergo absorption atelectasis resulting in shunt. Small airways lacking cartilage depend on radial traction of the lung to stay open, and this radial traction falls as lung volume falls.

### Closing Capacity

Closing capacity (CC) is the lung volume during expiration at which airways begin to close. FRC falls below CC resulting in airways closure in patients who are elderly, obese, or supine and anesthetized. FRC declines with supine position; CC does not. Approaching age 55, FRC falls below CC in the supine position resulting in a decrease in oxygenation.



## Hysteresis

The inflation and deflation characteristics of the lung are not identical. At a given volume the transmural pressure is higher during inflation and lower during deflation. The faster the volume is changed the greater the difference in pressure. This behavior is called hysteresis (Fig 2-4) and is caused predominantly by the surface tension at the gas liquid interface.

## Alveolar Ventilation

Several forms of ventilation are conventionally described. The total ventilation,  $V_E$ , is the volume of gas leaving the lung during expiration. Alveolar ventilation ( $V_A$ ) = total ventilation – dead space ventilation.

## Dead Space

A proportion of ventilation, *physiologic dead space*, does not participate in gas exchange. Physiologic dead space is the sum of anatomic and alveolar dead space. Anatomic dead space is the

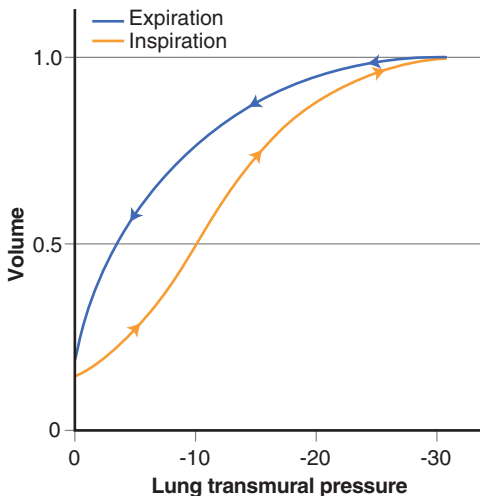


Figure 2-4 – Hysteresis.

volume of gas in the conducting airways. Alveolar dead space is the change in volume of gas in alveoli that are not functionally perfused. In health the alveolar dead space approximates zero and therefore physiologic and anatomic dead spaces are almost identical. When dead space is increased in disease, it is essentially always due to an increase in alveolar dead space.

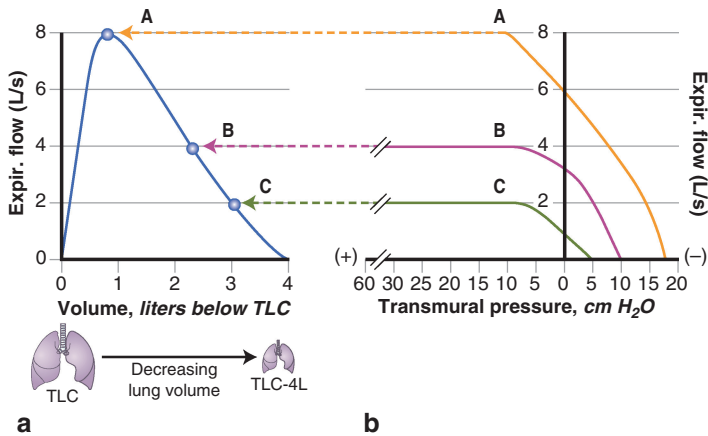
## Resistance and Gas Flow

Airway resistance is predominantly affected by airway cross-sectional area, which in turn is influenced by lung volume, elastic recoil, and airway smooth muscle tone. In any individual the primary modifiable determinant of airways resistance is lung volume. The intrinsic elastic properties of the lung cannot be changed. Therefore, maximum flows are greater at high lung volumes, and may be diminished by airway constriction or compression, secretions, foreign bodies, and increased lung water. In healthy subjects, intermediate-sized bronchi contribute most of the resistance to flow, and small airways contribute the least.

In a given airway, gas flow may be laminar or turbulent (3). Characteristics that promote turbulence include high flow rates, tubes that are not long and straight (i.e., curved, branching, changing in diameter), and fluids with high density or low viscosity. At a given flow turbulence is more likely in a smaller tube. In laminar flow states, the pressure drop required for a given flow is proportional to the flow, inversely proportional to the fourth power of the radius, the flow profile is parabolic with highest velocity in the center of the airway, and viscosity is the dominant fluid characteristic. Turbulent flow is less efficient, the pressure drop required for a given flow is proportional to the flow squared, inversely proportional to the fifth power of the radius, the flow profile is flat, and density is the dominant fluid characteristic.

## Expiratory Flow Limitation

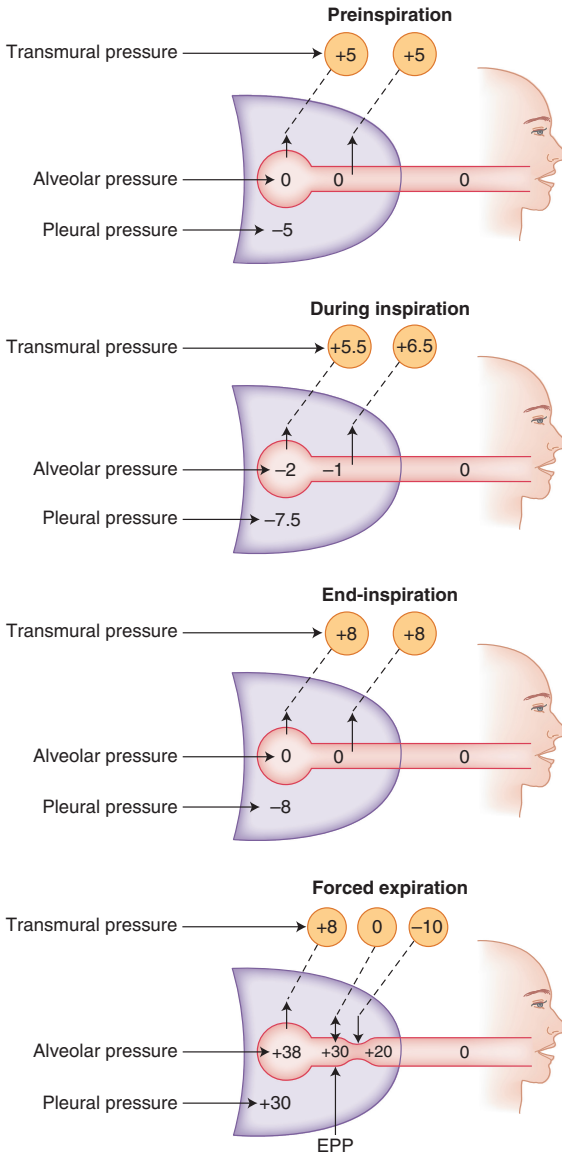
During expiration as lung volume falls so does elastic recoil and airway transmural pressure. Consequently, airway diameter decreases and resistance increases. Maximum expiratory airflow



**Figure 2-5** – (a) Expiratory phase of a flow-volume loop. (b) Expiratory flow becomes relatively fixed (independent of positive transmural pressure or effort) at different rates depending on lung volume (Compare A vs. B vs C). modified from West JB; Respiratory Physiology - the essentials (7th Edition) Lippencott, Williams & Wilkins, 2005.

falls and becomes “effort independent”; that is independent of increased effort beyond a modest threshold. These factors give rise to the characteristic outer envelope of the expiratory portion of the flow-volume loop. See Fig 2-5.

The mechanisms that limit maximum flow through compressible tubes, both airways and blood vessels, are complex. The *equal pressure point model* (Fig 2-6) describes the phenomenon in airways as follows. The pressure outside intrathoracic airways is  $P_{pl}$ , the pressure within the airway begins at alveolar pressure ( $P_{pl}$  + Lung elastic recoil pressure, which depends upon lung volume) and ends at zero (atmospheric) at the mouth. As gas flows from alveolus to mouth, the pressure within the airway falls due to resistance. Therefore, during a forced expiration the pressure within the airway will at some point equal  $P_{pl}$  (the equal pressure point). Downstream (mouthward) of the EPP the airway transmural pressure will be negative, and the airway is compressed. Increased expiratory effort increases  $P_{pl}$  but not lung elastic recoil pressure, further compressing the airway so flow does not increase. The loss of elastic recoil and therefore lung elastic recoil pressure in obstructive lung disease causes expiratory airflow limitation to become more severe and more



**Figure 2-6** – Flow limitation in a single alveolus (equal pressure point model).

heterogenous. This phenomenon is clinically relevant to obstructive pulmonary disease, and to air trapping, and its consequences.

## Work of Breathing

A variety of forces must be overcome to move gas, the lung, and chest wall. The work of breathing is the measure of work involved in overcoming these forces. The amount of work required is dependent on airways resistance (see above) and the physical properties of the tissues and liquids comprising and contained in the respiratory system, the gas that is being breathed, and the interfaces of gases, liquids, and tissues contained in the thorax.

## Diffusion

Gas transport across the alveolar wall is via passive diffusion. Diffusion rates are influenced by the partial pressure difference between alveolar gas and blood, the surface area of alveoli available for diffusion, the distance over which the gas must diffuse, the solubility of the gas in the alveolar wall, and their molecular weights.

In healthy lungs there is an estimated 50–100 m<sup>2</sup> of alveolar-capillary surface area, and the thickness of the tissue barrier through which gases must diffuse is less than half of a micrometer. Transit time of blood in the lung is determined by the ratio of pulmonary capillary volume to cardiac output. At rest blood spends approximately three-fourth of a second in the pulmonary capillaries.

Doubling cardiac output (e.g., exercise) does not halve transit time because the increased pulmonary artery pressure causes pulmonary capillary blood volume to increase by a combination of recruitment and distension. This design provides an enormous capacity for gas exchange, and in healthy individuals pulmonary end capillary blood and alveolar gas are in equilibrium for all gases even at high flows. *Gas exchange is rarely diffusion-limited.* Under rare circumstances, such as very high cardiac output states, transit time may be reduced enough that diffusion limitation becomes important.

$\text{CO}_2$  is much more soluble in water and tissue than  $\text{O}_2$ , and as a result,  $\text{CO}_2$  diffuses approximately 20 times faster. Consequently, diffusion limitation of carbon dioxide is even more uncommon than for oxygen.

Diffusing capacity (DL) of the lung is measured using uptake of carbon monoxide (CO) because of its very high affinity for hemoglobin. DLCO is measured as CO uptake ( $\dot{V}_{\text{CO}}$ )/alveolar partial pressure of CO ( $P_{\text{A}}\text{CO}$ ).

### Ventilation Perfusion Relationships

The respiratory system accomplishes exchange of gas by having blood and air in close proximity across a large diffusive surface area. Efficient exchange of oxygen and carbon dioxide depends on the regional matching of ventilation and perfusion in all areas of the lung. A spectrum of possible  $\dot{V}/\dot{Q}$  ratios exists within each of the roughly 480 million alveoli of the lung. At the extremes are shunt – a state of perfusion without ventilation ( $\dot{V}/\dot{Q}=0$ ), and dead space – ventilation without perfusion ( $\dot{V}/\dot{Q}=\text{infinity}$ ).

#### Shunt

The reader should note that shunt is variously used to refer to:

1. Pure or true shunt as defined above ( $\dot{V}/\dot{Q}=0$ )
2. The solution to the shunt equation for venous admixture or virtual shunt (see below)
3. Areas of very low  $\dot{V}/\dot{Q}$  ratios

The mixed venous blood that flows through true shunt mixes with pulmonary capillary blood and reduces the oxygen content of arterial blood. Increasing the  $\text{FiO}_2$  has no impact on the hypoxic effect of true shunt. Sources of shunt may be physiologic or pathologic (Table 2-1).

**Table 2-1 – Sources of true shunt**

## Physiologic shunt (1–3% of CO)

- Bronchial circulation
- Pleural circulation
- Thebesian veins

## Pathologic sources of shunt

- Intrapulmonary
  - Atelectasis
  - Intrapulmonary arteriovenous malformations
- Extrapulmonary
  - Cardiac right to left shunts (requires abnormal communication between right and left heart and elevated right heart pressure)

Arterial oxygen content is reduced by true shunt as well as perfusion of regions of low  $\dot{V}/\dot{Q}$  ratio. Examination of  $\text{PaO}_2$  or A-a gradient fails to distinguish these causes. The shunt equation quantifies the amount of shunt that would exist if true shunt alone explained the degree of arterial oxygen deficiency. Ventilation with 100%  $\text{O}_2$  will restore oxygenation in areas with very low  $\dot{V}/\dot{Q}$  ratios, and the shunt equation will yield a better estimate of true shunt. The shunt and dead space equation (see below) are derived from simplified two-compartment models where blood flow is either ideal or shunt, and ventilation is either ideal or dead space.

$$Q_s/Q_t = [(C_c'O_2 - CaO_2)/(C_c'O_2 - CvO_2)]$$

$Q_s$  = shunt blood flow;

$Q_t$  = total blood flow;

$C_c'O_2$  = end pulmonary capillary oxygen content;

$CaO_2$  = arterial oxygen content;

$CvO_2$  = mixed venous oxygen content.

## Dead Space

Like the term shunt, dead space is variously used to refer to:

1. Pure dead space as defined above ( $\dot{V}/\dot{Q} = \text{infinity}$ )
2. The solution to the dead space equation (see below) or virtual dead space
3. Areas of very high  $\dot{V}/\dot{Q}$  ratios

Dead space was defined earlier as the volume of gas that is not available for exchange with blood. Physiologic dead space is measured using the modified Bohr equation and is defined as  $V_D/V_T = (P_a\text{CO}_2 - P_E\text{CO}_2) / P_a\text{CO}_2$ .

$V_D$  = dead space ventilation;

$V_T$  = total ventilation;

$P_a\text{CO}_2$  = partial pressure of carbon dioxide in arterial blood;

$P_E\text{CO}_2$  = partial pressure of carbon dioxide in end tidal gas;

$P_a\text{CO}_2$  = partial pressure of carbon dioxide in arterial gas.

Physiologic dead space is composed of anatomic dead space and alveolar dead space which is usually negligible in health. Anatomic dead space is measured by the Fowler's method where a subject inspires a single breath of pure oxygen and the washout of dead space gas is plotted by the accumulation of nitrogen to a plateau consistent with that of pure alveolar gas and is approximately 2 ml/pound lean body weight.

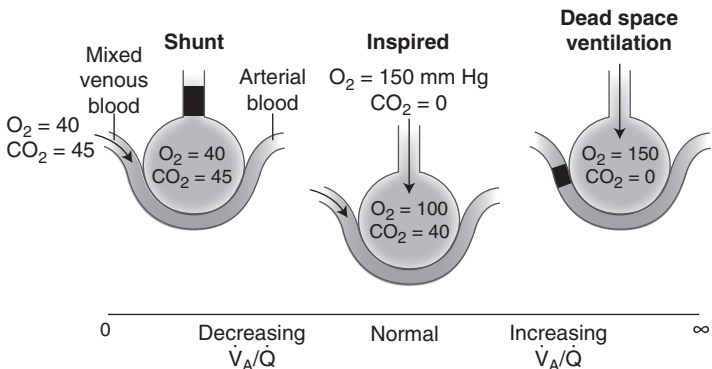
In normal upright subjects at rest, approximately 80% of ventilation and perfusion go to lung regions with a  $\dot{V}/\dot{Q}$  ratio of 0.3–1.0. Shunt predominantly affects oxygenation, demonstrated by a low  $P_a\text{O}_2$  due to a widening of the alveolar to arterial (A–a) gradient. An increase in alveolar dead space predominantly affects  $\text{CO}_2$  and is demonstrated by an increase in total ventilation needed to achieve a given  $P_a\text{CO}_2$ , due to a widening of the arterial to end-tidal gradient.



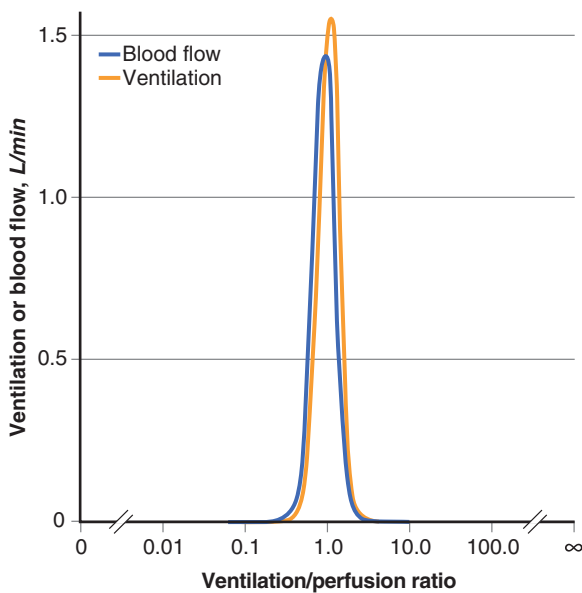
$\dot{V}/\dot{Q}$  heterogeneity always results in an increased (A–a) gradient because the oxyhemoglobin dissociation curve plateaus, and blood flow through regions with high  $\dot{V}/\dot{Q}$  ratios cannot compensate for the low  $O_2$  content of blood coming from lung regions with low  $\dot{V}/\dot{Q}$  ratios (Fig 2-7). However, the same is not true for  $CO_2$  because the  $CO_2$  content vs. partial pressure relationship is nearly linear.

Distribution of ventilation and perfusion is modeled using the multiple inert gas elimination technique (MIGET) in which six inert gases of different solubility are injected intravenously, and measured in arterial and mixed venous blood and expired gas. The lung is modeled as a set of 50 respiratory units, each with a different  $V/Q$  ratio. The amount of ventilation to regions of pure dead space, of perfusion to regions of pure shunt, and of ventilation and perfusion to lung regions with the intermediate values of  $\dot{V}/\dot{Q}$  matching can be graphically illustrated. MIGET diagrams thus subdivide the lung based on function ( $\dot{V}/\dot{Q}$  matching) rather than structure, and illustrate the functional distribution of ventilation and perfusion.

In Fig 2-8,  $\dot{V}/\dot{Q}$  relationships derived from MIGET are depicted in a young healthy patient in the upright position and breathing spontaneously. Note that ventilation and perfusion are tightly matched to one another, and exhibit little spread (dispersion) to regions of inefficient  $\dot{V}/\dot{Q}$  relationships.



**Figure 2-7** – Effects of different  $\dot{V}/\dot{Q}$  ratios.



**Figure 2-8** – Distribution of ventilation and perfusion in a patient aged 22 years.

The remarkable degree of  $\dot{V}/\dot{Q}$  matching normally achieved in the topographically complex lung is incompletely understood. Prominent mechanisms include gravity, HPV, and the congruence of the geometry between the pulmonary arterial and tracheo-broncheal arborizations.

### Gravitational Effects

Both perfusion and ventilation are greater in dependent portions of the lung due to gravity. Because blood has greater density than lung tissue, the effect on perfusion exceeds that on ventilation. While both  $\dot{Q}$  and  $\dot{V}$  increase from non-dependent regions to dependent regions,  $\dot{Q}$  increases faster, and the  $\dot{V}/\dot{Q}$  ratio falls. This results in lower  $\dot{V}/\dot{Q}$  ratios in dependent regions and higher ratios in nondependent regions.

The effects of gravity on regional distribution of local pulmonary artery and pulmonary vein pressure in relation to each other and

to alveolar pressure (the pressure outside pulmonary capillaries) result in a vertical gradient of flow. The effects are often described as West zones of the lung. There is no blood flow in zone 1 where  $P_{alv} > P_{pa} > P_{pv}$ . Moving down the lung, in zone 2 where  $P_{pa} > P_{alv} > P_{pv}$ , flow increases quickly as the driving pressure ( $P_{pa} - P_{alv}$ , *not*  $P_{pa} - P_{pv}$ ) increases, and the vessels become larger as the absolute intravascular pressure increases. Moving down the lung, in zone 3 where  $P_{pa} > P_{pv} > P_{alv}$ , flow increases slowly as driving pressure does not change (because  $P_{pa}$  and  $P_{pv}$  are increasing by the same amount), however, the vessels become larger as the absolute intravascular pressure increases.

The effects of gravity on ventilation are due to the vertical variation in  $P_{pl}$ . At FRC, dependent alveoli are smaller than nondependent ones due to the weight of the lung above. Because the lung sits in the chest and is affected by gravity, the weight of the lung causes the pleural pressure to be more negative in nondependent regions and less negative in dependent regions. However, alveolar pressure is the same throughout the lung. Hence, dependent lung regions are exposed to a lower transmural pressure, the alveoli are smaller, and are on a more compliant part of their pressure–volume curve. Inspiration results in greater increases in volume (more ventilation) of dependent alveoli compared to the already relatively expanded and less compliant nondependent alveoli.

There is little doubt that gravity affects both ventilation and perfusion in the same direction, and thus contributes to  $\dot{V}/\dot{Q}$  matching, but the magnitude of this effect remains a subject of debate (4).

## Anatomic Effects

Higher resolution studies than those done by West reveal isogravitational heterogeneity in regional pulmonary  $\dot{V}$  and  $\dot{Q}$ , in addition to the vertical heterogeneity described above (5). Within a horizontal plane the majority of ventilation and perfusion is located in the center of the lung with a decreasing gradient toward the periphery. Congruence between the geometry of the pulmonary arterial and bronchial arborizations likely contributes considerably to  $\dot{V}/\dot{Q}$  matching.

## Hypoxic Pulmonary Vasoconstriction

HPV is a physiologic response of the pulmonary arterioles to local alveolar hypoxia. HPV is only exhibited by the pulmonary circulation – other arterial beds dilate in response to hypoxemia.

The precise mechanism of HPV is still unknown. It is believed to be a phenomenon of smooth muscle cells in small ( $<500\ \mu\text{m}$ ) pulmonary resistance vessels, and involves hypoxia-triggered inhibition of voltage-gated potassium channels, membrane depolarization, and calcium release from sarcoplasmic reticulum. HPV is thought to function independently of endothelium but may be modulated at this level. Its onset occurs within seconds and has a time constant of about 150 s; 63% of the maximal effect will be reached within about 150 s and 95% in about 450 s (8 min) (6, 7).

The primary trigger to HPV is alveolar hypoxia; low mixed venous oxygen saturation acts as a secondary trigger. Pulmonary vascular resistance may increase up to three times baseline values due to widespread HPV. Regional or local HPV responses divert perfusion from hypoxic alveoli to better ventilated ones, powerfully fine tuning  $\dot{V}/\dot{Q}$  matching.

The effects of HPV are decreased by beta agonists, calcium channel blockers, inhalational agents, and nitrodilators. The effects of HPV are augmented by cyclo-oxygenase inhibitors, beta blockers, and the drug almitrine.

These mechanisms (gravitational, anatomic, HPV) are normally the most important agents influencing  $\dot{V}/\dot{Q}$  matching. Other influences impact the distribution of pulmonary perfusion and  $\dot{V}/\dot{Q}$  matching, including, but not limited to:

- Cardiac output
- Pulmonary artery pressure
- Local autocrine/paracrine molecules
  - Nitric oxide
  - Endothelin
  - Prostaglandins

- Thromboxane
- Leukotrienes
- Neural effects (autonomic and nonautonomic)
- Humoral agents (catecholamines, etc.)

Pulmonary pathophysiology and the perturbations of anesthesia, thoracic surgery, and one-lung ventilation impose considerable disruption of this complex balance, and impact efficiency of gas exchange (see Chapters 3–5).

## Gas Transport

Oxygen in the blood is carried both in a dissolved form and a more significant fraction that is bound to hemoglobin (Hb). Arterial oxygen content is calculated as:

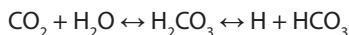
$$\text{CaO}_2 \text{ ml O}_2/\text{dl blood} = (1.34 \text{ ml O}_2/\text{gm Hb} \times \text{SaO}_2 \times \text{Hb}) + (0.003 \text{ ml O}_2/\text{dl/torr} \times \text{PaO}_2)$$

$\text{PaO}_2$  = partial pressure of oxygen in arterial blood in mmHg;

$\text{SaO}_2$  = arterial oxygen saturation

Oxygen saturation and hemoglobin concentration are the primary determinants of arterial oxygen content.

Carbon dioxide is carried in blood as bicarbonate, in a dissolved form, and in combination with proteins, of which Hb is the most significant. Bicarbonate carries the majority of  $\text{CO}_2$  although in venous blood it carries somewhat less than that in arterial blood. Bicarbonate formation from  $\text{CO}_2$  and water is shown below; the first step of which requires carbonic anhydrase.



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