Chapter 19

Respiratory Physiology and Pathophysiology

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Key Points

- Removal of CO_2 is determined by alveolar ventilation, not by total (minute) ventilation.
- Dead space ventilation can be dramatically increased in patients with chronic obstructive pulmonary disease and pulmonary embolism to more than 80% of minute ventilation.
- Breathing at small lung volumes increases airway resistance and promotes closure of airways.
- Hypoxemia can be caused by alveolar hypoventilation, diffusion impairment, ventilation-perfusion mismatch, and right-to-left shunt.
- Almost all anesthetics reduce skeletal muscle tone, which decreases functional residual capacity (FRC) to levels close to the awake residual volume (RV).
- Atelectasis during anesthesia is caused by decreased FRC and the use of high inspired oxygen concentrations (Fio_2), including breathing oxygen before induction of anesthesia.
- General anesthesia causes ventilation-perfusion mismatch (airway closure) and shunts (atelectasis).
- Venous admixture is due to $\dot{V}_A/\dot{Q}$ mismatch (response to increased Fio_2) and shunts (unresponsive to increased Fio_2).
- Hypoxic pulmonary vasoconstriction is blunted by most anesthetics, and this results in increased ventilation-perfusion mismatching.
- Respiratory work is increased during anesthesia as a consequence of reduced respiratory compliance and increased airway resistance.

RESPIRATORY PHYSIOLOGY IS CENTRAL TO THE PRACTICE OF ANESTHESIA

Respiratory function is inextricably linked to the practice of anesthesia. Adverse respiratory effects can occur during anesthesia,[1] and the most serious cases of adverse events involve hypoxemia. These events range from intractable hypoxemia caused by loss of airway patency to postoperative respiratory depression from opioids or regional anesthesia (see Chapter 96).[2,3] In the absence of adverse outcomes, general anesthesia has significant effects on respiratory function and lung physiology by observations made in the operating room. Improved appreciation of anesthesia-induced physiologic alterations (e.g., mechanisms of bronchospasm,[4] impact of mechanical ventilation),[5] as well as pioneering developments in monitoring (e.g., pulse oximetry and capnography; see Chapter 44),[6] together are associated with the specialty of anesthesiology's emergence as a leader in patient safety (see Chapter 6).[7] Finally, integrative measures of respiratory function, ranging from exercise capacity,[8] spirometry to tissue oxygenation,[9] or global O_2 consumption,[8] are likely predictors of outcome following anesthesia and surgery.

PULMONARY PHYSIOLOGY IN HEALTH

The mechanisms by which anesthesia-associated respiratory dysfunction are caused can be determined with an examination of the normal functions and mechanisms of respiration in health. We briefly review cellular respiration whereby O_2 is consumed and CO_2 is produced, the transport of O_2 and CO_2 in the blood, and the principles by which the lung oxygenates blood and eliminates CO_2.

RESPIRATION IN THE CELL

The partial pressure of oxygen (PaO_2) in normal arterial blood is approximately 100 mm Hg, and decreases to 4 to 22 mm Hg in the mitochondrion where it is consumed. Glucose ($C_6H_{12}O_6$) is converted into pyruvate (CH_3COCOO^-) and H^+ by glycolysis in the cytoplasm, and the pyruvate diffuses into the mitochondria and forms the initial substrate for Krebs cycle, which in turn produces nicotinamide adenine dinucleotide (NADH), as well as adenosine triphosphate (ATP), CO_2, and H_2O. The NADH is a key electron (and H^+) donor in the process of oxidative phosphorylation, wherein O_2 and adenosine diphosphate (ADP) are consumed and ATP and H_2O are produced. Thus, the net effect is oxidation of glucose to produce energy (ultimately as ATP), H_2O, and CO_2.[10]

TRANSPORT OF O_2 IN THE BLOOD

O_2 reaches the cells following transport by arterial blood, and the overall delivery of O_2 ($\dot{D}O_2$) is the product of the arterial blood O_2 content (CaO_2) and blood flow (cardiac output, $\dot{Q}$) as:

$$\dot{D}O_2 = CaO_2 \times \dot{Q}$$

The carriage in the blood is in two forms: O_2 bound to hemoglobin (the vast bulk), and O_2 dissolved in the plasma, and is expressed as the sum of these components as follows:

$$CaO_2 = \left[\begin{array}{l} (SaO_2 \times Hb \times O_2 \textit{ combining capacity of } Hb) \\ + (O_2 \textit{ solubility} \times Pao_2) \end{array} \right]$$

where CaO_2 (O_2 content) is the milliliters of O_2 per 100 mL of blood, SaO_2 is the fraction of hemoglobin (Hb) that is saturated with O_2, O_2-combining capacity of Hb is 1.34 mL of O_2 per gram of Hb, *Hb* is grams of Hb per 100 mL of blood, Pao_2 is the O_2 tension (i.e., dissolved O_2), and solubility of O_2 in plasma is 0.003 mL of O_2 per 100 mL plasma for each mm Hg Pao_2

The binding of O_2 to hemoglobin is a complex, allosteric mechanism. Important insights can be gained by understanding how characteristic abnormalities of blood O_2 carriage (e.g., carbon monoxide [CO] poisoning, methemoglobinemia) affect on O_2 tension, content, and delivery.

Methemoglobin (MetHb), formed by the oxidation to Fe^{3+} (ferric) instead of the usual Fe_2^+ (ferrous), is less able to bind O_2, resulting in diminished O_2 content and less O_2 delivery. Here, the Pao_2 (in the absence of lung disease) will be normal: if the O_2 content is calculated from the Pao_2, it will appear normal, but if measured it will be low. In contrast, MetHb level will be elevated. In severe cases, lactic acidosis develops because of impaired O_2 delivery. In addition, because MetHb has a blue-brown color, the patient will appear blue, even if the fraction of MetHb is modest and specialized oximetry can separately measure MetHb levels.[11,12] The apparent cyanosis is not responsive to supplemental O_2, and therapy involves converting (i.e., reducing) the MetHb to Hb (e.g., by using methylene blue). Important medical causes of MetHb include benzocaine; dapsone; or in susceptible patients, inhaled nitric oxide (NO).

In CO poisoning, the CO binds to Hb, with far greater (over ×200-fold) avidity than molecular O_2, tightly forming CO-Hb and resulting in two main effects.[13] First, formation of CO-Hb results in fewer sites available for O_2 binding, and this reduces the blood O_2 content. Second, the formation of CO-Hb causes conformational changes in the Hb molecule such that the tendency to release bound O_2 is reduced. This effect corresponds to a leftward shift of the Hb-O_2 dissociation curve, and although this aspect of CO binding does not reduce the O_2 content or "global" delivery of O_2, it does reduce the release of O_2 and its delivery to the cells. Because the color of CO-Hb closely resembles that of O_2-Hb, the color of the blood (and the patient) is bright red; however, as with Met-Hb, the PaO_2 will be normal (assuming no pulmonary disease) as will the calculated CaO_2; however, the measured CaO_2 will be low and if severe, a lactic acidosis will be present. Modern can distinguish between Hb-O_2 and CO-Hb.[13]

Finally, the *Bohr effect* refers to a shift of the Hb-O_2 dissociation curve caused by changes in CO_2 or pH.[14] In the systemic capillaries, the Pco_2 is higher than in the arterial blood (and the pH correspondingly lower) because of local CO_2 production. These circumstances shift the Hb-O_2 dissociation curve to the right, which increases the offloading of O_2 to the tissues. The opposite occurs in the pulmonary capillaries; the $Paco_2$ is lower (and the pH correspondingly higher) because of CO_2 elimination, and the dissociation curve is shifted to the left to facilitate O_2 binding to Hb.

TRANSPORT OF CO_2 IN THE BLOOD

CO_2 is produced by metabolism in the mitochondria, where the CO_2 levels are highest. The transport path (involving progressively decreasing pressure gradients) is from mitochondria through cytoplasm, into venules and finally, in mixed venous blood from where it is eliminated through the alveoli. In the blood, CO_2 is transported in three main forms: dissolved (reflected as $Paco_2$, partial pressure; accounts for approximately 5% of transported CO_2), bicarbonate ion (HCO_3^-; almost 90%), and carbamino CO_2 (CO_2 bound to terminal amino groups in Hb molecules; approximately 5%).[10] The usual quantities of CO_2 in the arterial and (mixed) venous blood are approximately 21.5 and 23.3 mmol of CO_2 per liter of blood, respectively.

Breathing O_2 can sometimes induce hypercapnia, as occurs in patients with severe chronic lung disease who are breathing supplemental O_2. Although traditionally thought to occur because increased Pao_2 reduces ventilatory drive, this is now known not to be the case[15]; it results from the Haldane effect, as well as from impairment of hypoxic pulmonary vasoconstriction (HPV). The Haldane effect[16] is the difference in the amount of CO_2 carried in oxygenated versus deoxygenated blood, and two mechanisms explain this. First, increased Pao_2 decreases the ability to form carbamino compounds—reducing the amount of CO_2 bound to Hb—thereby raising the amount of dissolved CO_2 (i.e., elevated Pco_2). Second, the amino acid histidine, which has an imidazole group that is an effective H^+ buffer at physiologic pH, is an important linking molecule between heme groups

and the Hb chains. Increasing the partial pressure of oxygen (PO_2) increases the amount of O_2 bound to Hb; this changes the conformation of the Hb molecule, which in turn alters the heme-linked histidine and reduces its H^+ buffering capacity. Therefore, more H^+ is free (not buffered) and binds to HCO_3^-, releasing stored CO_2. Impairment of HPV by elevated O_2 allows increased perfusion to poorly ventilated regions; this has the effect of decreasing perfusion (and delivery of CO_2) to better ventilated regions, diminishing the efficiency of CO_2 elimination. Patients with impaired ability to increase alveolar ventilation ($\dot{V}_A$) cannot compensate for the increased CO_2 availability, and therefore, in these patients, adding supplemental O_2 can result in elevated Pa_{CO_2}.

OXYGENATION IN THE PULMONARY ARTERY

Systemic venous blood (central venous blood) enters the right ventricle via the right atrium. The O_2 saturation (SO_2) differs among the major veins: higher venous SO_2 reflects greater blood flow, less tissue oxygen uptake, or both.[17] SO_2 is usually higher in the inferior vena cava (IVC) than in the superior vena cava (SVC), possibly because of the high renal and hepatic flow relative to O_2 consumption. In the right ventricle, the central venous blood ($S_{cv}O_2$) from the SVC and IVC, is joined by additional venous blood from the coronary circulation (via the coronary sinuses). In the right ventricle, an additional small amount of venous drainage from the myocardium enters through the Thebesian veins, and as all this venous blood enters the pulmonary artery it is well mixed and is termed *mixed-venous blood* ($S_{\bar{v}}O_2$); thus, $S_{\bar{v}}O_2 < S_{cv}O_2$, although the trends of each usually run in parallel.[18]

VENTILATION

Ventilation refers to the movement of inspired gas into and exhaled gas out of the lungs.

ALVEOLAR VENTILATION

Fresh gas enters the lung by cyclic breathing at a rate and depth (tidal volume, V_T) determined by metabolic demand, usually 7 to 8 L/min.[19] While most inspired gas reaches the alveoli, some (100 to 150 mL) of each V_T remains in the airways and cannot participate in gas exchange. Such dead space (V_D) constitutes approximately one third of each V_T.[20] Anatomic V_D is the fraction of the V_T that remains in the "conducting" airways, and physiologic V_D is any part of a V_T that does not participate in gas exchange (Fig. 19-1).

For a single tidal volume (V_T, mL), the following is true:

$$V_T = V_A + V_D$$

The product of V_T (mL) times the respiratory rate (per minute) is the minute ventilation ($\dot{V}_E$). Aggregated over time, minute ventilation ($\dot{V}_E$, mL/min) is:

$$\dot{V}_E = \dot{V}_A + f \times V_D$$

The portion of the $\dot{V}_E$ that reaches the alveoli and respiratory bronchioles each minute and participates in gas exchange is called the *alveolar ventilation* ($\dot{V}_A$), and it is approximately 5 L/min. Because this is similar to the blood flow through the lungs (i.e., the cardiac output, also 5 L/min), the overall alveolar ventilation-perfusion ratio is approximately 1.

DEAD SPACE VENTILATION

Maintenance of Pa_{CO_2} is a balance between CO_2 production ($\dot{V}CO_2$, reflecting metabolic activity) and alveolar ventilation ($\dot{V}_A$. If $\dot{V}_E$ is constant but V_D is increased, $\dot{V}_A$ will naturally be reduced, and the Pa_{CO_2} will therefore rise. Therefore, if V_D is increased, $\dot{V}_E$ must also increase to prevent a rise in Pa_{CO_2}. Such elevations in V_D occur when a mouthpiece or facemask is used, and in such cases, the additional V_D is termed "apparatus deadspace" (which can be up to 300 mL; anatomic V_D of the airways is 100 to 150 mL).[21]

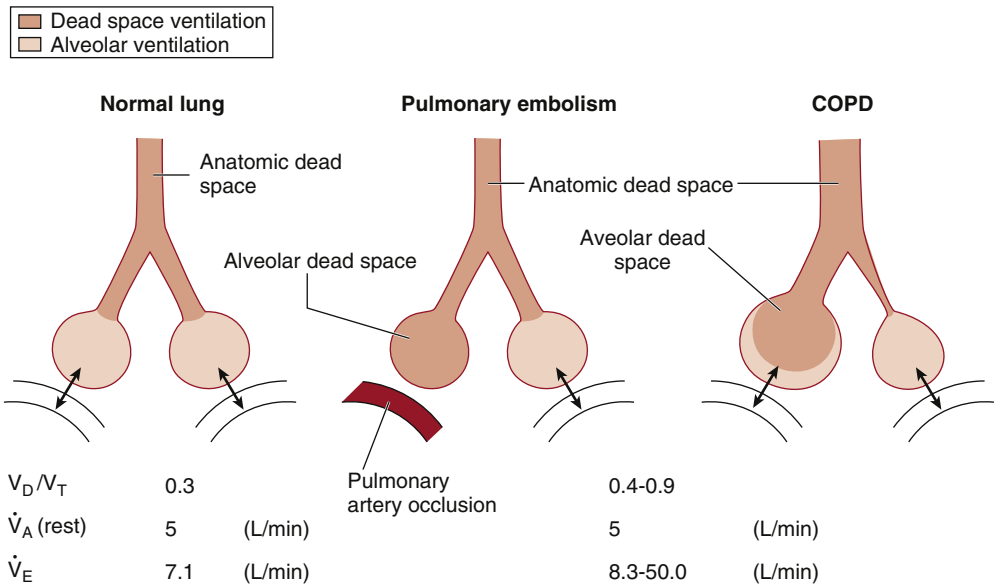


Figure 19-1. Dead space and alveolar ventilation in normal and diseased lungs. Either cessation of blood flow or excessive alveolar ventilation relative to perfusion will cause an increase in dead space. If V_D is increased, a large compensatory increase in minute ventilation is required to preserve $\dot{V}_A$. V_D/V_T, dead space to tidal volume ratio; $\dot{V}_A$, alveolar ventilation; $\dot{V}_E$, minute ventilation. $\dot{V}_E = \dot{V}_A + f \times V_D$. *Double arrows* indicate normal CO_2 exchange. *COPD*, Chronic obstructive pulmonary disease. *(From Hedenstierna G: Respiratory measurement. London, 1998, BMJ Books, 1998, p. 184; see also book review of* Respiratory Measurement in Thorax *53:1096, 1998.)*

Increases in the volume of the conducting airways (e.g., bronchiectasis) increase the overall V_D only slightly. Far more significant increases in V_D occur when perfusion to a large number of ventilated alveoli is interrupted, as occurs in a pulmonary embolus (see Fig. 19-1). Indeed, with multiple pulmonary emboli, V_D/V_T can exceed 0.8 (2.7-fold normal). In such a case, to maintain a normal $\dot{V}_A$ (5 L/min), the $\dot{V}_E$ would have to increase (also 2.7-fold) to almost 20 L/min. This effort would cause considerable dyspnea, in addition to the dyspnea induced by the lowered PaO_2.

Obstructive lung disease can result in diversion of inspired air into (nonobstructed) ventilated, but poorly perfused, regions of the lung. This results in local excesses of ventilation versus perfusion (high $\dot{V}_A/\dot{Q}$ ratio) in such regions,[22] which is equivalent to an increase in V_D/V_T (see Fig. 19-1). Patients with severe chronic obstructive pulmonary disease (COPD) may have a V_D/V_T ratio of up to 0.9, and would have to hyperventilate massively (30 to 50 L/min) to maintain normal $Paco_2$, which is not possible where ventilator reserve is diminished. Such patients demonstrate reduced $\dot{V}_A$ but often have an elevated $\dot{V}_E$. An important compensatory mechanism is that a lower level of $\dot{V}_A$ will maintain stable CO_2 excretion where the $Paco_2$ is increased (Box 19-1).

STATIC LUNG VOLUMES—FUNCTIONAL RESIDUAL CAPACITY

The amount of air in the lungs after an ordinary expiration is called *functional residual capacity* (Fig. 19-2); it is usually 3 to 4 L and occurs because of the balance of inward (lung) forces and outward (chest wall) forces. The inward force is the "elastic recoil" of the lung and emanates from the elastic lung tissue fibers, contractile airway smooth muscle, and alveolar surface tension. The outward force is developed by passive recoil from the ribs, joints, and muscles of the chest wall. FRC is greater with increased height and age (loss of elastic lung tissue), and smaller in women and in obesity (see Chapter 71).[19,23]

There are two reasons why maintenance of gas in the lung at end-expiration (i.e., FRC) is important. First, inflating an already opened (inflated) lung is easier than when the lung is already deflated. This is because complete collapse results in liquid-only surfaces interfacing in alveoli (high surface tension), whereas alveoli in partially inflated lung have air-liquid interfaces (lower surface tension). Second, although perfusion in the lung is phasic, the frequency is rapid and the oscillations in flow are low, resulting in nearly continuous flow. Ventilation is different: the frequency is far slower and the size of the oscillations far larger. If the lung (or large parts of it) completely deflate between breaths, the blood flowing from closed alveoli (that contain zero O_2) would have very low SO_2 (the same as mixed venous blood); this would mix into the overall blood flow from the lungs and cause a major O_2 desaturation after every exhalation.

RESPIRATORY MECHANICS

The study of respiratory mechanics tells us how inspired air is distributed within the lung and permits quantitation of the severity of lung disease. The components of overall impedance to breathing results from elastance (the reciprocal of compliance), resistance, and inertia.

COMPLIANCE OF THE RESPIRATORY SYSTEM

The lung is like a rubber balloon that can be distended by positive pressure (inside) or negative pressure (outside). Under normal circumstances, inflation of the lung is maintained because although the pressure inside (alveolar pressure) is zero, the outside pressure (i.e., the pleural pressure) is sufficiently negative. The net distending pressure, which is the difference of the (positive) airway pressure (P_{AW}) and the (negative) pleural pressure (P_{PL}) is termed the *transpulmonary pressure* (P_{TP}). Thus:

$$P_{TP} = P_{AW} - P_{PL}$$

Clearly, increasing the P_{AW} increases the P_{TP}. In addition, lowering the P_{PL} (which is usually negative and making it more negative) making it more negative) also increases the P_{TP}.

Compliance—the reciprocal of elastance—is the term that expresses how much distention (volume in liters) occurs for a given level of P_{TP} (pressure, cm H_2O); it is usually 0.2 to 0.3

BOX 19-1 *Alveolar Gas Equations*

Alveolar Oxygen Tension (P_{AO_2})

$$P_{AO_2} = P_{IO_2} - \frac{P_{ACO_2}}{R} + \left[P_{ACO_2} \times FiO_2 \times \frac{1-R}{R}\right]$$

where P_{IO_2} is inspired oxygen tension, P_{ACO_2} is alveolar CO_2 tension (assumed to equal arterial Pco_2), R is the respiratory exchange ratio (normally in the range of 0.8 to 1.0), and FiO_2 is the inspired oxygen fraction. The term within brackets compensates for the larger O_2 uptake than CO_2 elimination over the alveolar capillary membranes.

A simplified equation can be written without the compensation term:

$$P_{AO_2} = P_{IO_2} - \frac{P_{ACO_2}}{R}$$

Alveolar Ventilation

Alveolar ventilation ($\dot{V}_A$) can be expressed as

$$\dot{V}_A = f \times (V_T - V_{DS})$$

where f is breaths/min, V_T is tidal volume, and V_{DS} is physiologic dead space.

Alveolar ventilation can also be derived from:

$$\dot{V}_{CO_2} = c \times \dot{V}_A \times F_{ACO_2}$$

where $\dot{V}_{CO_2}$ is CO_2 elimination, c is a conversion constant, and F_{ACO_2} is the alveolar CO_2 concentration.

If $\dot{V}_A$ is expressed in L/min, $\dot{V}_{CO_2}$ in mL/min, and F_{ACO_2} is replaced by P_{ACO_2} in mm Hg, $c = 0.863$. By rearranging:

$$\dot{V}_A = \frac{\dot{V}_{CO_2} \times 0.863}{P_{ACO_2}}$$

L/cmH_2O.[24] However, although higher values of P_{TP} maintain greater levels of lung opening, the relationship—as with most elastic structures—between applied pressure and resultant volume is curvilinear (Fig. 19-3).[24] Lung compliance depends on the lung volume; it is lowest at an extremely low or high FRC (see Fig. 19-3). In lung diseases characterized by reduced compliance (e.g., ARDS, pulmonary fibrosis or edema), the pressure-volume curve is flatter and shifted to the right (Fig. 19-4).[24] In contrast, although emphysema involves the loss of elastic tissue, the overall loss of lung tissue (as seen on computed tomography [CT] scanning)[25] means that the compliance is increased; the pressure-volume curve is therefore shifted to the left and is steeper (see Fig. 19-4).[24]

The chest wall impedance is not noticed during spontaneous breathing because the respiratory "pump" includes the chest wall. Chest wall mechanics can be measured only if complete relaxation of the respiratory muscles can be achieved[26]; however, during mechanical ventilation the respiratory muscles can be completely relaxed. As the lung is inflated by P_{AW}, the properties of the chest wall will determine the resulting change in P_{PL}. Under these circumstances, the increase in lung volume per unit increase in P_{PL} is the chest wall compliance. Values of chest wall compliance are about the same as that of the lung and are reduced with obesity, chest wall edema, pleural effusions, and diseases of the costovertebral joints.[26]

RESISTANCE OF THE RESPIRATORY SYSTEM

Airways

Resistance impedes airflow into (and out of) the lung. The major component of resistance is the resistance exerted by the airways (large and small), and a minor component is the sliding of lung and the chest wall tissue elements during inspiration (and expiration).[27] Resistance is overcome by (driving) pressure. In spontaneous breathing, driving pressure will be the P_{PL}; in positive pressure ventilation, the

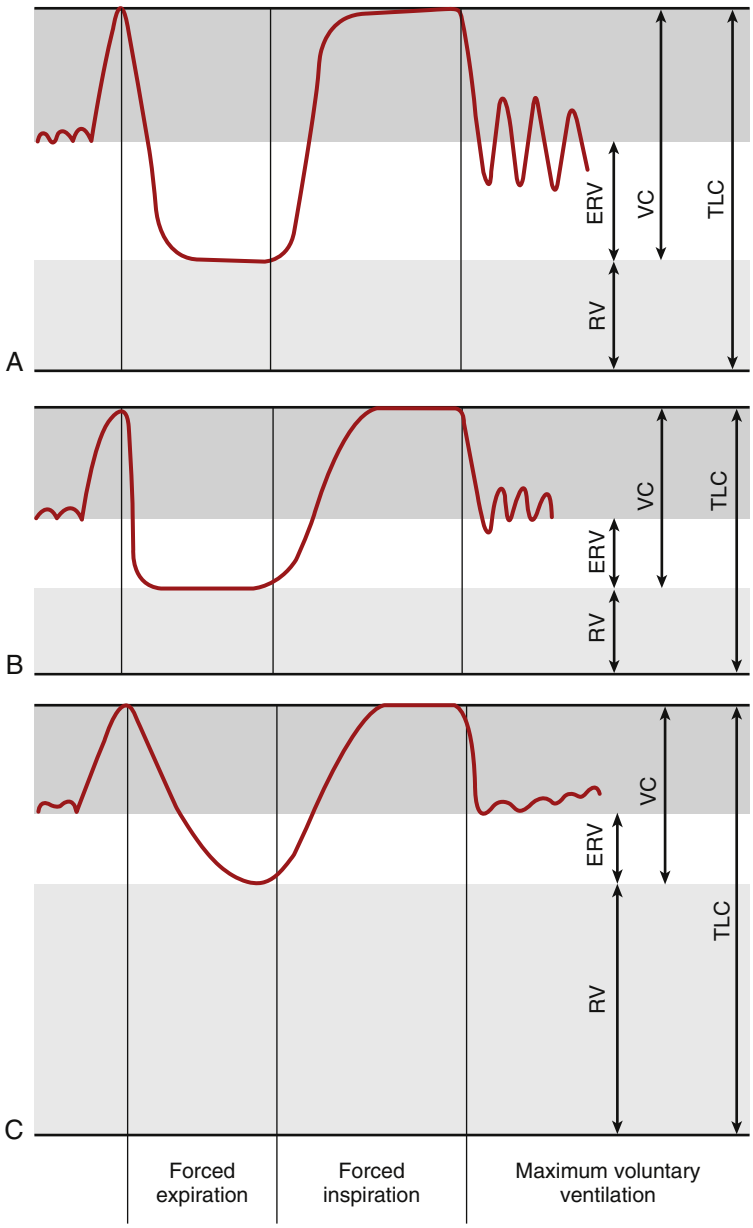


Figure 19-2. A, Ventilation and lung volumes in a healthy subject with normal lungs. **B,** A patient with restrictive lung disease. **C,** A patient with chronic obstructive pulmonary disease (COPD). In restrictive disease, the vital capacity (VC) is decreased and expiratory flow rate is increased (i.e., steeper than the normal slope of the forced expiratory curve). In COPD, the residual volume (RV) is increased, the VC is reduced, and forced expiration is slowed. *ERV,* Expiratory reserve volume; *TLC,* total lung capacity. *(From Hedenstierna G: Respiratory measurement. London, 1998, BMJ Books, 1998, p. 184; see also book review of* Respiratory Measurement in Thorax *53:1096, 1998.)*

driving pressure will be difference between the pressures applied to the endotracheal tube (P_{AW}; "source") and the alveolus (P_{ALV}; "destination"). Resistance (R) is calculated as driving pressure (ΔP) divided by the resultant gas flow (F):

$$R = {}^{\Delta P}/_{F}$$

The value of airway resistance is approximately 1 cm H_2O/L/sec, and is higher in obstructive lung disease (e.g., COPD, asthma); in severe asthma, it is elevated approximately tenfold.[28] The presence of an endotracheal tube adds a resistance of 5 (or 8) cm H_2O/L/min for a tube with internal diameter of size 8 (or 7) cm.[29] For any tube for which the airflow is laminar (smooth, streamlined), the resistance increases in direct proportion to the tube length and increases dramatically (to the fourth power) as the diameter of the tube is reduced.

Two factors explain why most (approximately 80%) of the impedance to gas flow occurs in the large airways.[27] First, as bronchi progressively branch, the resistances are arranged in parallel and the total cross-sectional area at the level of the terminal bronchioles adds up to almost tenfold that at the trachea. Second, in tubes that are large, irregular or branched, the flow is often turbulent, not laminar. When flow is laminar:

$$F_{(lam)} = {}^{\Delta P}/_{R}$$

In contrast, when flow is turbulent:

$$F_{(turb)} = {}^{\Delta P}/_{R^2}$$

Therefore, for a given radius, far more pressure is required to achieve comparable flow where flow is turbulent; thus, the effort required is greater and if prolonged or severe, respiratory failure is more likely.

Several factors can alter airflow resistance. First, resistance lessens as lung volume increases; this is intuitive as increasing volume (positive pressure or spontaneous breathing) stretches the diameter of the airways; because this is the key determinant of resistance, the resistance falls to a small extent. The opposite occurs with exhalation (Fig. 19-5). However, as lung volume approaches RV—as can happen during anesthesia—the airways are narrowed in parallel with the compressing lung tissue and the resistance rises

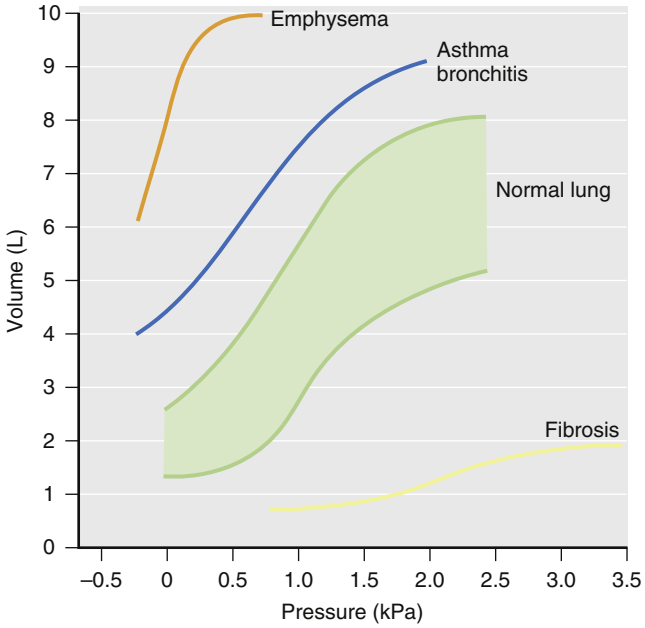


Figure 19-4. Pressure-volume curves of the lung in health and lung disease. In fibrosis, the slope of the curve is flatter, reflecting considerable increases in pressure variation and in respiratory work. In asthma or bronchitis, there is a parallel (upward) shift of the pressure-volume curve, indicating an increase in lung volume but no change in compliance. In emphysema, the slope of the curve is steeper, reflecting tissue loss and possible increased compliance. However, in emphysema, asthma, or bronchitis, the airway resistance is increased; this increases work of breathing and overrides any benefit from increased compliance. *(From Hedenstierna G: Respiratory measurement. London, 1998, BMJ Books, 1998, p. 184; see also book review of* Respiratory Measurement in Thorax *53:1096, 1998.)*

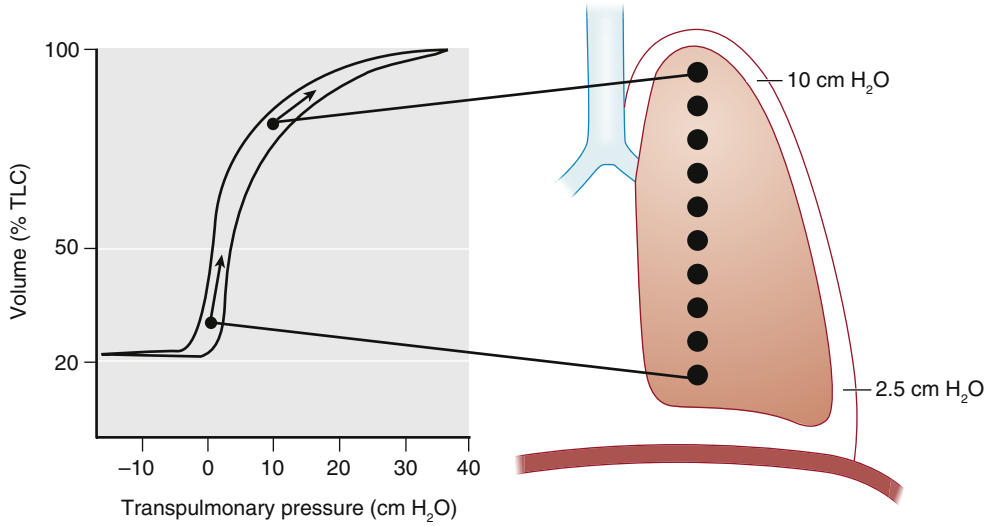


Figure 19-3. The pressure-volume relationships of the lung. The relationship is curvilinear (typical for an elastic structure). The pleural pressure is lower (more subatmospheric) in the upper regions. In the upright subject, the transpulmonary pressure ($P_{TP} = P_{AW} - P_{PL}$) is higher in apical than in basal regions. This results in different positions on the pressure volume curve of the upper (flatter, less compliant) versus lower (steeper, more compliant) lung regions. Thus, lower lung regions expand more (i.e., receive more ventilation) for a given increase in transpulmonary pressure than upper units. *TLC,* Total lung capacity.

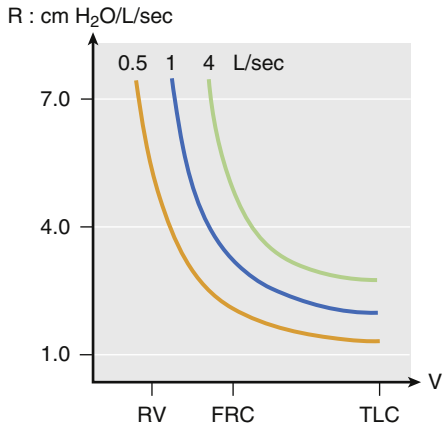


Figure 19-5. Schematic drawing of airflow resistance against lung volume at different flow rates. As lung volume falls, the resistance to flow increases; the steepness of this increase is far greater at lung volumes below functional residual capacity (FRC). In addition, higher airflow rates are associated with greater resistance. At extremely low lung volume, the resistance is comparable to values seen in moderate to severe asthma (6 to 8 cm $H_2O \times l^{-1} \times$ sec). *RV,* residual volume; *TLC,* total lung capacity.

exponentially. These effects are apparent with active or passive ventilation. Second, active ventilation has additional effects. Forced expiration can compress small airways (i.e., that do not contain cartilage).[27] In addition, forced expiration can cause turbulent flow in small airways in patients with COPD, precipitously dropping pressure in the lumen and thereby narrowing the bronchioles[30] and resulting in expiratory flow limitation and, after multiple breaths, eventual "dynamic hyperinflation."[31] Expiring against resistance (or pursed-lips breathing) is sometimes used by those with COPD to make breathing easier. This works by increasing expiratory resistance and slowing expiration. The slowed expiration reduces the pressure gradient driving expiration (i.e., pressure highest in the alveolus, lower toward the mouth). Therefore, the point along the airway tree at which pressure inside the airway has decreased to less than that outside the airway (equal to pleural pressure) is moved from smaller collapsible airways toward the mouth to noncollapsible, cartilaginous airways (Fig. 19-6); this prevents collapse of the smaller airways, which are vital for proper gas exchange.[32]

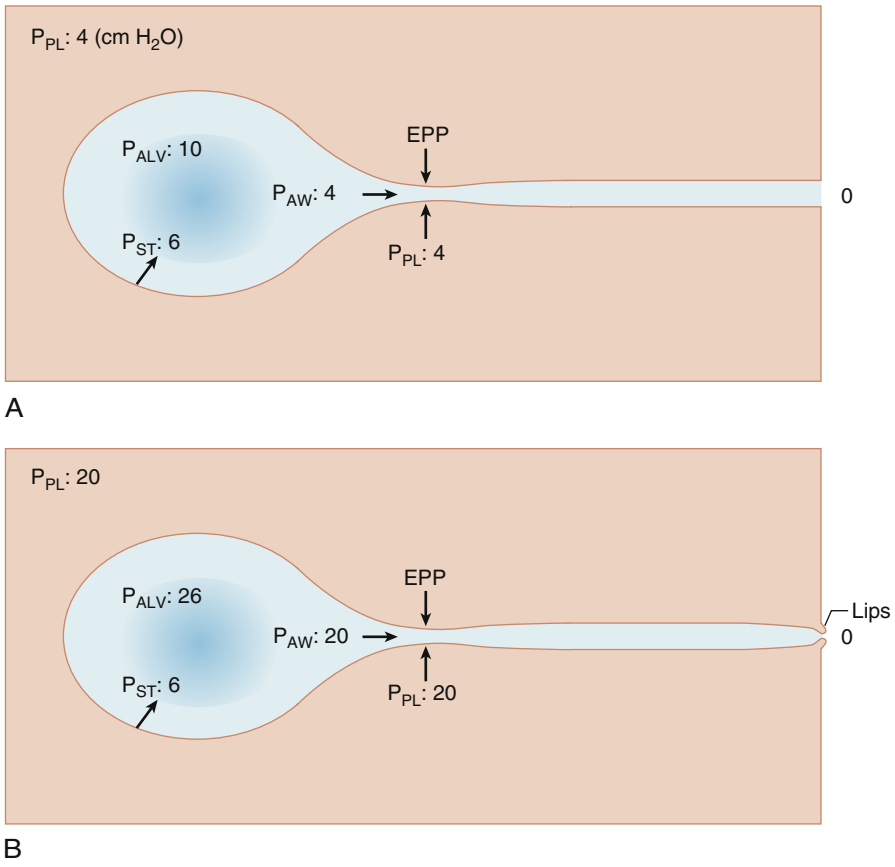


Figure 19-6. Schematic drawings of the equal pressure point (EPP) concept and dynamic compression of airways. **A,** Slightly forced expiration during otherwise normal conditions. With the application of some expiratory muscle effort, pleural pressure (P_pl) is positive, 4 cm H_2O (0.4 kPa). The elastic recoil pressure (Pst) of the alveoli (6 cm H_2O) and the pleural pressure add together to yield intraalveolar pressure (Palv) (10 cm H_2O). This causes expiratory flow. At some point downstream toward the airway opening, airway pressure (Paw) has dropped by 6 cm H_2O, so intraluminal pressure and pleural, extraluminal pressure are the same. This is the EPP. From this point to the mouth, intraluminal airway pressure is lower than the surrounding, extraluminal pressure and the airway may be compressed. **B,** An attempt to stabilize the airway by so-called "pursed-lip" breathing. The increased resistance to expiratory flow requires increased expiratory effort to maintain gas flow. Thus, pleural pressure is increased in comparison to the normal conditions (Ppl = 20 cm H_2O). Alveolar elastic recoil pressure (Pst) is the same as in the earlier condition, provided that lung volume is the same. If expiratory flow is of the same magnitude as during normal breathing, pressure along the airway falls to the same extent as during normal breathing. Thus the EPP will have the same location as during normal breathing, and no stabilization of the airway has been achieved. The two ways of moving the EPP toward the mouth and to less collapsible airways is by raising alveolar recoil pressure (Pst) by an increase in lung volume or by lowering the expiratory flow rate so that the pressure drop along the airway tree is slowed down.

The large airways (i.e., pharynx, larynx, and trachea) are outside the chest wall. During inspiration, the intrathoracic airways are exposed to extraluminal pressure (i.e., P_{PL}) that is less than the lumen pressure; in contrast, the extrathoracic airways are exposed to lumen pressure that is less than the extraluminal (i.e., atmospheric) pressure.[27] This feature, coupled with downward stretch induced by inspiration, narrows the large extrathoracic airways; in the presence of preexisting narrowing (e.g., thyroid enlargement or tumor, paralyzed vocal cord, epiglottitis), it can critically reduce the cross-sectional area.

Tissue

Although not intuitively obvious, resistance of the lung tissue is the applied pressure on tissue divided by the resulting velocity of tissue movement. There are various approaches to determining this in humans, including separately considering the pressure-volume (PV) characteristics using plethysmography (where the area of the PV curve corresponds to work against total pulmonary resistance) and esophageal pressure (where the area of the PV curve corresponds to work against "tissue" resistance).[33] Alternative approaches mathematically model the lung responses to varying respiratory frequencies.[34] Lung tissue resistance amounts to 20% of the total resistance to breathing; it can be increased threefold or fourfold in chronic lung disease[35] and is reduced by panting respirations.[36] Finally, in ARDS the chest wall resistance is increased (see Chapter 103).[37]

INERTIA OR ACCELERATION OF GAS AND TISSUE

A final component of the total impedance to breathing is inertance, or the pressure required to accelerate air and tissue during inspiration and expiration. This component is minor, however, and can hardly be measured under normal breathing, regardless of whether the lungs are healthy. Nonetheless, tissue inertia is large during rapid ventilation,[38] and it could be important during the rapid, shallow breathing characteristic of weaning failure or during high-frequency oscillation.

DISTRIBUTION OF INSPIRED GAS

Inspired gas is not evenly distributed throughout the lung; naturally, more gas enters those lung units that expand most during inspiration. In the resting lung, the basal (dependent) regions are less aerated than the apical (nondependent) regions; therefore, they have the capacity to undergo greater expansion. During inspiration, most gas goes to the basal units (dorsal, when supine; lower right lung when in the right lateral position).[39] This distribution is because of the compliance properties of the lung and the effects of position on the distribution of the distending pleural pressure (i.e., the P_{PL} gradient). These changes are not related to the properties of the inspired gas.

In the upright position, the P_{PL} is less negative at the base of the lung than at the apex. Because the P_A is uniform throughout the lung, the distending P_{TP} is greater at the apex; therefore, before inspiration commences, the apical lung is more open (and is less compliant) than the basal lung (Figs. 19-3 and 19-7). With inspiration, the contracting diaphragm lowers the P_{PL} by a comparable amount in all areas of the pleural surface (because of the fluid-like behavior of normal lung[39]) and distends the basal more than the apical regions (see Figs. 19-3 and 19-7). Because the pleural pressure gradient is oriented according to gravity, the distribution of ventilation changes with body position.

The P_{PL} gradient exists because lung density, gravity, and conformation of the lung to the shape of the thorax[40] result in crowding the basal lung tissue, making the local P_{PL} less negative in the basal regions. Because the density of normal lung is approximately 0.3, P_{PL} will become more positive by 0.3 cm H_2O for each downward vertical centimeter, and more so with injured or edematous lungs. Indeed, experimentally induced weightlessness decreases inhomogeneity in the distribution of ventilation[41], but does not eliminate it; therefore, nongravitational (e.g., tissue, airway) factors also play a role.[42]

Although the vertical height of the lung is the same in the prone and supine positions, the vertical gradient P_{PL} is less when prone,[43] perhaps because the mediastinum compresses the dependent lung when supine but rests on the sternum when prone.[44] A more even distribution of inspired gas—with improved oxygenation—in the prone position was predicted by Bryan in 1974[44]; this has been confirmed experimentally.[45,46]

During low-flow states (e.g., at rest) distribution is determined by differences in compliance and not by airway resistance. Because compliance at the start of inflation is less in the (already more aerated) apex, ventilation is preferentially directed to the base. In contrast, at high airflow, resistance (not compliance) is the key determinant of distribution; because the resistance is lower in upper, more expanded lung regions, increasing flow rate equalizes the distribution of ventilation, as shown by distribution of ^{133}Xe gas in humans[47,48] (Fig. 19-8). This is important during exercise or stress because greater amounts of the alveolar-capillary surface area will be used.

AIRWAY CLOSURE

Expiration causes the airways to narrow, and deep expiration can cause them to close. The volume remaining above RV where expiration below FRC closes some airways is termed *closing volume* (CV), and this volume added to the RV is termed the *closing capacity* (CC; i.e., the total capacity of the lung at which closing can occur).[49] Closure of airways during expiration is normal and is potentiated by increasing P_{PL}, especially with active expiration. When P_{PL} exceeds the P_{AW}, the airway—if collapsible—will tend to close, and this usually commences at the bases because the basal P_{PL} is greatest (see Fig. 19-7).

Three applications of this important principle are of key relevance to anesthesia. First, airway closure depends on age: in youth, the closure does not occur until expiration is at or near RV, whereas with older age, it occurs earlier in expiration (i.e., at higher lung volumes). This occurs because P_{PL} is on average more "positive"

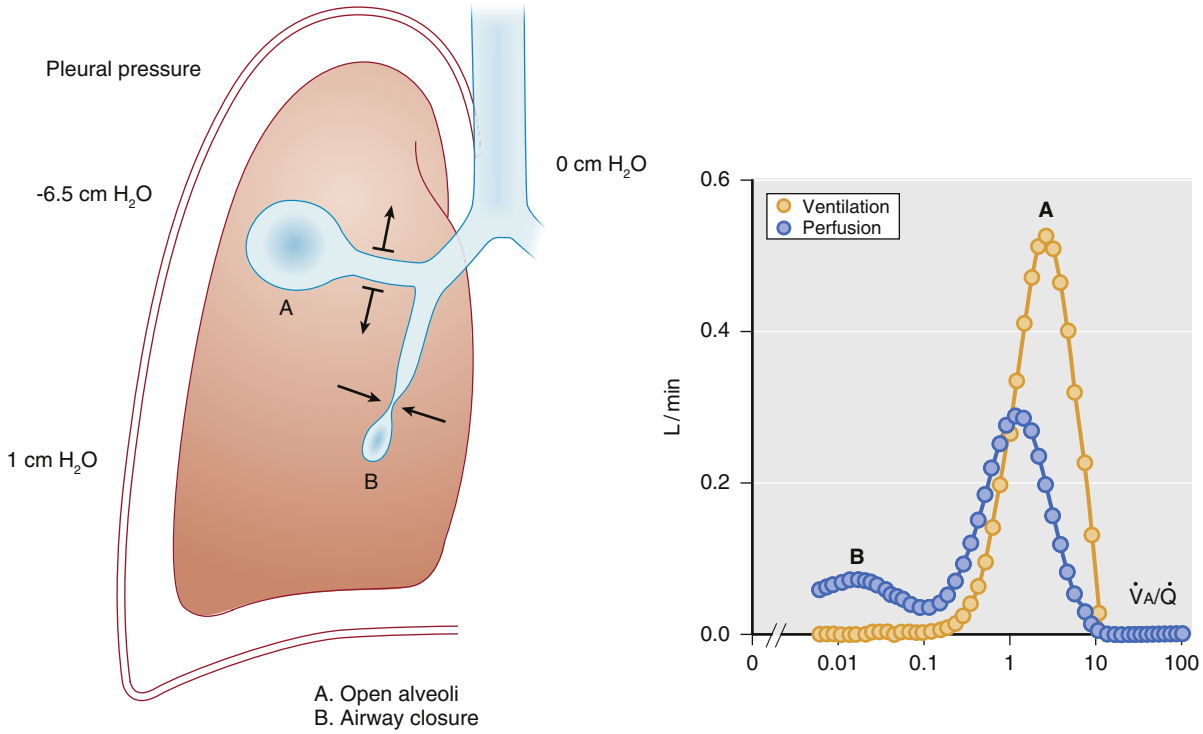


Figure 19-7. Schematic of regional alveolar and airway volume at an upper (*A*) and a lower (*B*) lung level (*left panel*). There is a vertical pleural pressure (P_{PL}) gradient between the uppermost and lowermost regions (–6.5 to 1 = –7.5 cm H_2O). Airway pressure (P_{AW}) is athmospheric, or 0 cm H_2O throughout; thus, in the upper regions, $P_{AW} > P_{PL}$ maintains airways open. In contrast, in the lower regions, $P_L > P_{AW}$ causes airway closure—potentially exacerbated by subsequent alveolar gas absorption behind the occluded airway. The *right panel* shows the distribution of ventilation and perfusion ratios from the multiple inert gas elimination technique. A "normal" mode of ventilation and blood flow (*A*) can be seen corresponding to the open and ventilated alveoli in the upper parts of the lung. In addition there is a range of low $\dot{V}_A/\dot{Q}$ ratios with more perfusion than ventilation (*B*). This pattern is compatible with intermittent airway closure during breathing.

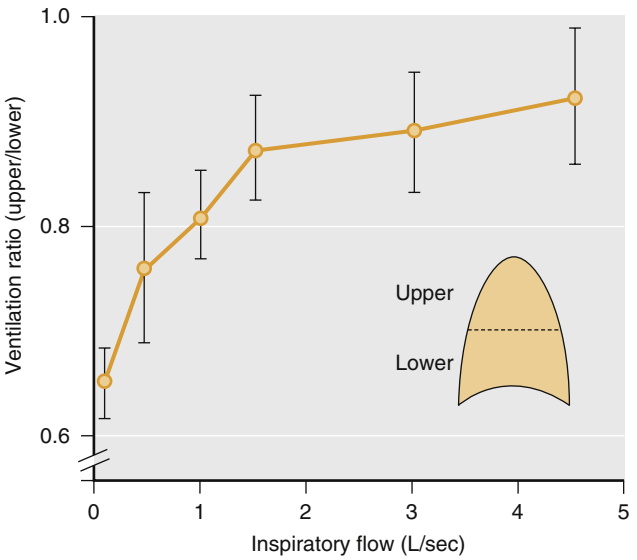


Figure 19-8. Distribution of ventilation to upper versus lower lung regions as inspiratory flow is altered. At low flow, the bulk of the airflow goes to the lower regions. At higher flow rates (e.g., during exercise) the distribution is more even, ensuring more efficient use of all alveolar-capillary membranes for gas transfer (provided that pulmonary blood flow shows a similar distribution pattern).

(i.e., atmospheric, equal to P_{AW}) as age increases. Closing can occur at or above FRC in individuals aged 65 to 70 years[50] such that dependent regions will undergo closure during normal expiration. This may be the major reason why oxygenation decreases with age (see Chapter 80). Second, in the supine position FRC is less than when upright, but CC is unchanged; therefore, exhalation of a usual V_T (from FRC) encroaches on CC in a supine 45 year old, and closure may be continuous in a supine 70 year old (Fig. 19-9). Finally, COPD increases the lung volume at which closure occurs, possibly exacerbated by airway edema and increased bronchial tone.[49]

DIFFUSION OF GAS

Gas moves in the large and medium-sized airways by bulk flow (i.e., convection) meaning that the gas molecules travel together at a given mean velocity according to a driving pressure gradient. Flow is through multiple generations of bronchi, and the net resistance falls with each division. After the fourteenth generation, airways merge with alveoli and participate in gas exchange (respiratory bronchioles). The cross-sectional area expands massively (trachea, 2.5 cm^2; twenty-third generation bronchi, 0.8 m^2; alveolar surface, 140 m^2),[51] resulting in a sharp drop in overall resistance. Because the number of gas molecules is constant, the velocity falls rapidly, which by the time the gas enters the alveoli is miniscule (0.001 mm/sec) and is

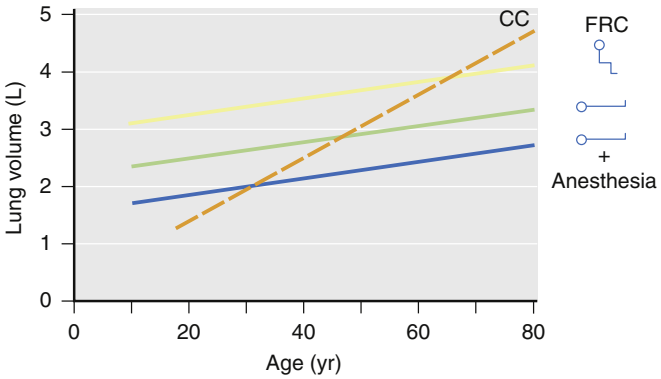


Figure 19-9. Resting functional residual capacity (FRC) and closing capacity (CC). FRC increases with age (because of loss of elastic tissue), and superimposed upon this is a step decrease in FRC with supine position (because of diaphragm elevation by abdominal contents), and a further decrease with anesthesia in the supine position. The CC is also increased with age, but far more steeply, causing airway closure above FRC in upright subjects (>65 yr) and in supine subjects (>45 yr). This relationship between CC and FRC explains decreasing oxygenation with age.

zero when it reaches the alveolar membrane. The velocity of the gas entering the alveolus is slower than the diffusion rates of O_2 and CO_2; therefore, diffusion—not convection—is necessary for transport in the distal airways and alveoli. Indeed, CO_2 is detectable at the mouth after just seconds of breath holding, because of rapid diffusion and because of cardiac oscillations (i.e., mixing).

Gas mixing is complete in the alveoli of a normal lung during normal breathing. However, if the alveolus expands (e.g., emphysema), the diffusion distance may be too great to allow complete mixing, potentially leaving a layer of CO_2-rich gas lining the alveolar membrane and a core of O_2-rich gas in the alveolus. This represents a "micro" version of inhomogeneous distribution of ventilation.[52]

PERFUSION

The pulmonary circulation differs from the systemic circulation: it operates at a five fold to tenfold lower pressure, and the vessels are shorter and wider. There are two important consequences of the particularly low vascular resistance. First, the downstream blood flow in the pulmonary capillaries is pulsatile, in contrast to the more constant systemic capillary flow.[53] Second, the capillary and alveolar walls are protected from exposure to high hydrostatic pressures; therefore, they can be sufficiently thin to optimize diffusion (i.e., exchange) of gas but not permit leakage of plasma or blood into the airspace. Whereas an abrupt increase in the pulmonary arterial (or venous) pressure can cause breaks in the capillaries,[54] slower increases (i.e., months to years) stimulate vascular remodeling.[55] This remodeling might protect against pulmonary edema[56] (and possibly against lung injury[57]), but diffusion will be impaired.

DISTRIBUTION OF LUNG BLOOD FLOW

Pulmonary blood flow depends on driving pressure and vascular resistance; these factors (and flow) are not homogenous

$$\text{Pulmonary vascular resistance (PVR)} = \frac{\bar{P}_{PA} - P_{LA}}{\dot{Q}_T}$$

(true only if lung is in zone III)

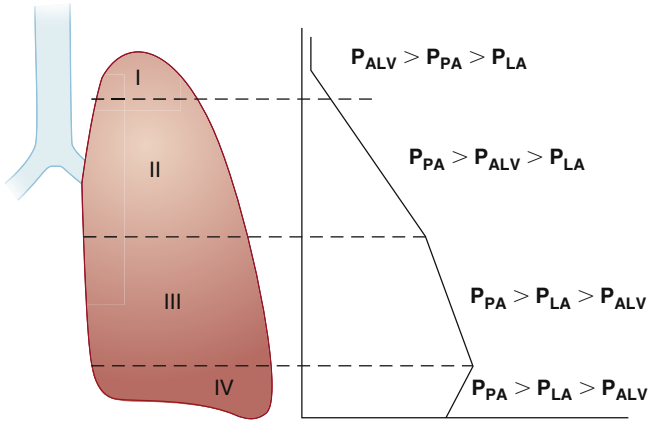


Figure 19-10. Vertical distribution of lung blood flow. The so-called zones I, II, III, and IV are indicated. In zone I there is no perfusion, only ventilation. In zone II, pulmonary artery pressure exceeds alveolar pressure which in turn exceeds venous pressure; the driving pressure is P_{PA}-P_A. In zone III, arterial and venous pressures both exceed alveolar pressure, and here the driving pressure is P_{PA}-P_{LA}. In the lung base, blood flow is decreased possibly because of increased interstitial pressure that compresses extra alveolar vessels. P_A, Alveolus pressure; P_{ALV}, positive intraalveolar pressure; P_{LA}, positive artery pressure; P_{PA}, pulmonary artery pressure; Q_T, cardiac output.

throughout the lung. The traditional thinking about lung perfusion emphasized the importance of gravity[58]; however, factors other than gravity are also important.

DISTRIBUTION OF BLOOD FLOW IN THE LUNG: THE EFFECT OF GRAVITY

Blood has weight and therefore blood pressure is affected by gravity. The height (base to apex) of an adult lung is approximately 25 cm; therefore, when a person is standing, the hydrostatic pressure at the base is 25 cm H_2O (i.e., approximately 18 mm Hg) higher than at the apex. The mean pulmonary arterial pressure is approximately 12 mm Hg at the level of the heart, and the pulmonary artery pressure at the lung apex can therefore approach zero. Thus, less blood flow will occur at the apex (versus the base), and in the setting of positive pressure ventilation, the apical alveoli can compress the surrounding capillaries and prevent any local blood flow.

Based on such gravitational distribution of pulmonary artery pressure, as well as the effect of alveolar expansion, West and colleagues[59] divided the lung into zones I to III (Fig. 19-10). This system is based on the principle that perfusion to an alveolus depends on the pressures in the pulmonary artery (P_{PA}), pulmonary vein (P_{PV}), and alveolus (P_{ALV}). In the apex (zone I), the key issue is that pulmonary arterial pressure is less than alveolar pressure; therefore, no perfusion occurs. Zone I conditions can exist during mechanical ventilation and be exacerbated by low P_{PA}. Whenever zone I conditions exist, the nonperfused alveoli constitute additional dead space (V_D).

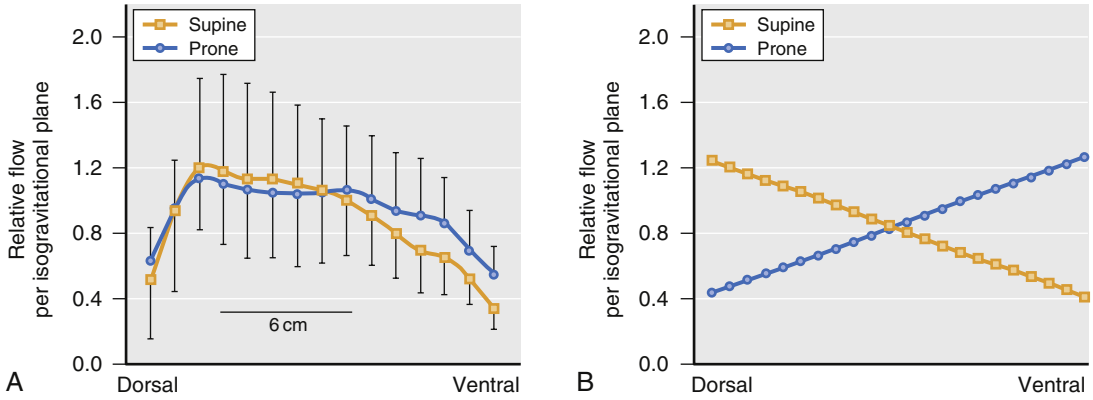


Figure 19-11. Distribution of blood flow (ventral, dorsal) in supine versus prone position. The distributions from ventral to dorsal are similar, irrespective of position, suggesting that that anatomic features (and not simply gravity) determine the distribution of flow. The magnitude of the variability in either the prone (or in the supine) position (i.e., nongravitational inhomogeneity) is far greater than the differences in distribution between the prone and the supine positions (i.e., gravitational inhomogeneity). *(From Glenny RW et al: Gravity is a minor determinant of pulmonary blood flow distribution,* J Appl Physiol *71:620-629, 1991.)*

Below the apex in zone II, P_{PV} is less than alveolar pressure, and the veins are collapsed except during flow, as in a "vascular waterfall." Although P_{ALV} is always greater than P_{PV}, perfusion occurs when P_{PA} exceeds P_{ALV} (i.e., intermittently, during systole). Below this zone is zone III, in which there are two important differences: P_{PA} and P_{PV} both always exceed P_{ALV}. As a result, there is perfusion throughout systole and diastole (and inspiration and expiration). Gravity results in equal increases in both P_{PA} and P_{PV} toward the lung base; therefore, gravity cannot affect flow throughout zone III by increasing the P_{PA} to P_{PV} pressure gradient alone. Nonetheless, it is possible that the greater weight of the blood nearer the base results in vessel dilatation, thereby lowering vascular resistance and increasing flow.[58] It was subsequently recognized that there is also a decrease in perfusion in the lung base, or zone IV, that is thought to occur because of the effects of gravity compressing the lung at the bases—and the blood vessels therein—and thereby increasing vascular resistance.[60]

Finally, additional evidence for the effect of gravity comes from volunteer experiments in which gravity was increased or abolished by altering the flight pattern of a jet aircraft.[61] In these experiments, zero gravity decreased cardiac oscillations of O_2 and CO_2 during a breath hold, indicating development of more homogeneous perfusion. In contrast, more recent experiments of exhaled gas analysis (on the Mir space station) reported that the heterogeneity of lung perfusion was reduced, but not eliminated, in the presence of microgravity, indicating that gravity contributes to the heterogeneity of blood flow distribution but does not explain it entirely.[62] While the precise role of gravity is disputed, it is likely to play a smaller role when supine versus when upright.

DISTRIBUTION OF BLOOD FLOW IN THE LUNG: INFLUENCE OF FACTORS NOT RELATED TO GRAVITY

Key experiments have reconsidered the effects of gravity. Blood flow measured in the same gravitational plane was less per unit of lung tissue at the apex than at the base.[63] In addition, microsphere assessment demonstrated significant variability within iso-gravitational planes, and lung height appeared to account for less than 10% of the distribution of flow in either the prone or supine positions.[64] In addition, inhomogeneity in the horizontal planes can exceed that in the vertical direction (Fig. 19-11).[65] Other studies have reported a preponderance of perfusion to the central lung (versus peripheral) tissue,[66] which can be reversed by the application of positive end-expiratory pressure (PEEP).[67] Although greater length of radial blood vessels was considered to explain this central-peripheral difference, others have suggested that it is not significant.[64] Finally, differences have been reported among lung regions in local vascular resistance.[68]

Fractal distribution of blood flow may be more important than the influence of gravity.[69] A fractal pattern of perfusion means that in any given region, there will be "spatial correlation" (similarity) of the blood flow between neighboring regions.

Although the methods to study lung perfusion are complex—and there is a spectrum of opinion[71,72], the aggregate data suggest that factors other than gravity contribute to the heterogeneity of the distribution of perfusion.

HYPOXIC PULMONARY VASOCONSTRICTION

Hypoxic pulmonary vasoconstriction is a compensatory mechanism that diverts blood flow away from hypoxic lung regions toward better oxygenated regions.[73] The major stimulus for HPV is low alveolar oxygen tension (P_AO_2), whether caused by hypoventilation or by breathing gas with a low PO_2, and is more potent when affecting a smaller lung region. The stimulus of hypoxic mixed venous blood is weaker.[74,75] Whereas in humans older volatile anesthetics were thought to inhibit HPV more than intravenously based anesthesia (in humans), modern volatile anesthetics, including sevoflurane[76] and desflurane,[77] have little effect. During intravenously based anesthesia, exposure of one lung to an Fio_2 of 1.0 and the contralateral to a hypoxic gas mixture (Fio_2, 0.12 to 0.05) reduced perfusion to the hypoxic lung to 30% of

the cardiac output.[78] Pulmonary hypertension, because of vascular remodeling owing to ongoing HPV, can develop in humans at high altitude[79] or in the presence of chronic hypoxemic lung disease.

CLINICAL ASSESSMENT OF LUNG FUNCTION

SPIROMETRY—TOTAL LUNG CAPACITY AND SUBDIVISIONS

The gas volume in the lung after a maximum inspiration is called the *total lung capacity* (TLC; usually 6 to 8 L). TLC can be increased in COPD either by overexpansion of alveoli or by destruction of the alveolar wall, resulting in loss of elastic tissue, as in emphysema (see Fig. 19-4).[80] In extreme cases, TLC can be increased to 10 to 12 L. In restrictive lung disease, TLC is reduced, reflecting the degree of fibrosis, and can be as low as 3 to 4 L (see Fig. 19-4).[80]

Following maximum expiratory effort, some air is left in the lung and constitutes the RV (about 2 L). However, usually no region develops collapse because distal airways (<2 mm) close before alveoli collapse,[81] trapping gas and preventing further alveolar emptying. In addition, there is a limit to how much the chest wall, rib cage, and diaphragm can be compressed. The importance of preventing collapse of lung tissue was presented earlier (see Fig. 19-6).

The maximum volume that can be inhaled and then exhaled is the vital capacity (VC; 4 to 6 L), and this is the difference between TLC and RV. VC is reduced in both restrictive and obstructive lung disease. In restriction, VC reduction reflects the loss of lung volume, such as from the constricting (i.e., shrinking) effects of fibrosis. In obstructive lung disease, long-term trapping of air increases the RV and can occur either by encroaching on (and reducing) the VC or in association with a (proportionally smaller) increase in FVC.[80]

Tidal volume (V_T, usually 0.5 L) is inspired from the resting lung volume reached at end-expiration (FRC, 2.0 L). With increased ventilation, as in exercise, V_T is increased and FRC may be reduced by approximately 0.5 L. However, in airway obstruction, exhalation is impeded such that inspiration commences before the usual resting lung volume is reached; thus end-expiratory volume is increased.[80] Such air trapping reduces the resistance to gas flow in the narrowed airways, but because the lung tissue is hyperinflated and mechanically disadvantaged, the work of breathing overall is increased (also see Chapter 103).

FRC increases with age as elastic lung tissue is lost; this reduces the lung recoil force countering the outward chest wall force, and lung assumes a higher volume (see Chapter 80). The rate of this aging process is accelerated in COPD because of the contributions of chronic air trapping and marked loss of elastic tissue.[19] FRC is reduced in fibrotic lung diseases,[80] sometimes to 1.5 L (see Fig. 19-4). Lung resection also reduces FRC, but the remaining lung will expand to fill the lung tissue void partially; this is called *compensatory emphysema* (see Chapter 66).

DIFFUSING CAPACITY (DL_{CO})—DIFFUSION ACROSS ALVEOLAR-CAPILLARY MEMBRANES

The diffusing capacity test integrates many phenomena that are central to respiratory physiology. The test and the factors affecting its interpretation are described here. In the lungs, O_2 and CO_2 diffuse passively: O_2 from alveolar gas into plasma and red cells, where it binds to hemoglobin, and CO_2 in the opposite direction, from plasma to the alveoli. The amount that can diffuse across a membrane in a given period is the diffusing capacity, and it is determined with the following equation:

$$Diffusing\ capacity = \frac{(SA \times \Delta P \times Sol)}{\left(h \times \sqrt{MW}\right)}$$

where SA is the surface area of the membrane exposed to gas, ΔP is the gradient of partial pressure between administered gas vs. blood tension, Sol is the solubility of the gas in the membrane, h is the thickness of the membrane, and MW is the molecular weight of the gas.

Assessment of diffusing capacity (sometimes called *transfer factor*) uses CO as the test gas; it is inhaled at a small concentration (0.3%) to TLC just after a maximal expiration, filling the lung as much as possible with the dilute CO. The breath is held and then deeply exhaled to RV. The difference between the quantity of CO exhaled versus inhaled will therefore either be taken up by the perfusing blood (i.e., Hb) or remain in the lung (RV). The latter can be determined if the CO is coadministered with an insoluble gas (e.g., He) that remains in the lung.

Surface Area

The surface area is taken as the area that is capable of exchanging gas on the alveolar and the capillary sides; thus, it assumes a ventilated and perfused lung (i.e., not dead space). It will be lower in small lungs, lung fibrosis (restriction), after lung resection, or in cases of lung tissue destruction, such as emphysema.

Membrane Thickness

Thicker membranes reduce the CO transfer because the longer diffusion distance lowers the diffusion capacity, and the solubility of O_2 (and CO_2) is lower in fibrotic tissue than in plasma. Differentiating between effects of the volume of capillary blood and the membrane thickness can be difficult, but because oxygen and CO compete for binding to hemoglobin, distinguishing between these issues may be possible by measuring CO transfer with altered Fio_2 (see review by Hughes and colleagues[82,83]).

Pressure Gradient

The larger the O_2 or CO_2 tension difference (ΔP) between the gas phase (alveolus) and the plasma (capillary), the greater the rate of diffusion. The mixed venous blood entering the pulmonary capillary has a PO_2 of 40 mm Hg (5.3 kPa), and alveolar PO_2 is approximately 100 mm Hg (13.3 kPa); therefore, the driving pressure (ΔP) is 60 mm Hg (8 kPa).

When blood flows through the capillary, it takes up oxygen and delivers CO_2, but because oxygen pressure

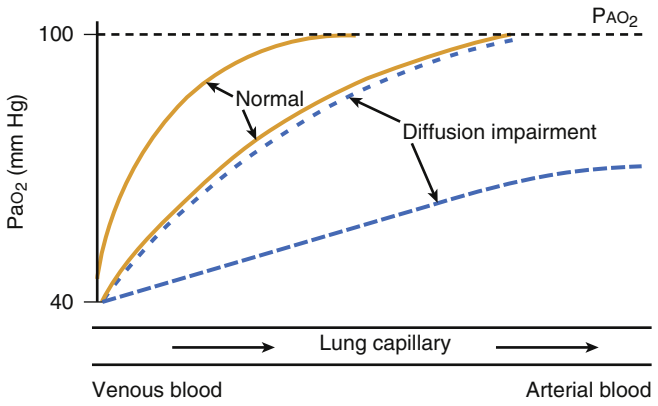


Figure 19-12. Schematic of oxygenation of pulmonary capillary blood. In a healthy subject, there is a rapid equilibration (<30% capillary length) of the oxygen tension in capillary blood with that in alveolar gas; however, during exercise, the flow rate is greater (i.e., transit time shorter) and most of the capillary distance is used before equilibration is reached. This effect can be offset by distention and recruitment of pulmonary capillaries. If diffusion is impaired, equilibration takes longer, and it might not occur with exercise.

builds up in capillary blood, the diffusion rate slows down and becomes zero when pressure is equilibrated across the alveolar-capillary wall. At rest, equilibrium is usually reached within 25% to 30% of the capillary length, and almost no gas transfer occurs in the remaining capillary (Fig. 19-12). However, during exercise or stress (i.e., high cardiac output), blood flow through the capillary is faster, and a longer capillary distance is required before equilibrium is reached. Thickened alveolar-capillary membranes will also prolong the equilibration process and, if severe, can prevent equilibration occurring and increasing the propensity to hypoxemia. If the mixed venous PO_2 ($P_{mv}O_2$) is lower than normal, the driving pressure increases and partially compensates towards achieving equilibrium with alveolar O_2. The driving pressure is expressed:

$$\Delta P = (PaO_2 - P_{mv}O_2)\ mm\ Hg$$

Most of the oxygen that dissolves in plasma diffuses into the red cell and binds to hemoglobin; therefore, 1 L of blood (Hb 150 g/L) with a saturation of 98%—normal in arterial blood—carries 200 mL of Hb-bound O_2, compared with 3 mL that is dissolved (PaO_2 100 mm Hg). The Hb-bound oxygen creates no pressure in plasma, which is important because it allows much more oxygen to diffuse over the membranes before a pressure equilibration is reached. Anemia (or prior CO exposure) reduces—and polycythemia increases—diffusion capacity.

Molecular Weight and Solubility

The rate of diffusion of a gas is inversely related to the square root of its molecular weight (MW); the larger the molecule, the slower the diffusion. O_2 is a light gas (MW 32) and CO_2 is heavier (MW 44). However, diffusion is also directly proportional to solubility in tissue, and CO_2 is almost thirtyfold times more soluble than O_2. The aggregate effect is that CO_2 diffuses about twentyfold faster than O_2[84]; therefore, there is no lung disease compatible with life that measurably impairs CO_2 diffusion.

INTRAOPERATIVE RESPIRATORY EVENTS

RESPIRATORY FUNCTION DURING ANESTHESIA

Anesthesia impairs pulmonary function, whether the patient is breathing spontaneously or is receiving mechanical ventilation. Impaired oxygenation of blood occurs in most subjects who are anesthetized,[85] and this is why supplemental O_2 (Fio_2 usually 0.3 to 0.5) is almost invariably used. Mild to moderate hypoxemia (SaO_2, 85% to 90%) is common and lasts from seconds to minutes; sometimes it is severe, and approximately 20% of patients may suffer from SaO_2 less than 81% for up to 5 minutes.[86] Indeed, greater than 50% of claims in anesthesia-related deaths relate to hypoxemia during anesthesia.[2] Beyond the operating room, the alterations in lung function acquired during anesthesia persist: clinically significant pulmonary complications can be seen in 1% to 2% patients after minor surgery, and in up to 20% of patients after more major upper abdominal or thoracic surgery.[87] Such consequences of anesthesia place prime importance on ascertaining the causes of perioperative respiratory dysfunction and the clinical approaches to treatment.

In this section, we describe the effects of anesthesia and mechanical ventilation on lung function. The arrangement of this section parallels the sequence of events involved in oxygenating the blood and removing CO_2. Thus, the first phenomenon that might be seen with anesthesia is loss of muscle tone with a subsequent change in the balance between outward forces (i.e., respiratory muscles) and inward forces (i.e., elastic tissue in the lung) leading to a fall in FRC. This causes or is paralleled by an increase in the elastic behavior of the lung (reduced compliance) and an increase in respiratory resistance. The decrease in FRC affects the patency of lung tissue with the formation of atelectasis (made worse with the use of high concentrations of inspired oxygen) and airway closure. This alters the distribution of ventilation and matching of ventilation and blood flow and impedes oxygenation of blood and removal of carbon dioxide.

LUNG VOLUME AND RESPIRATORY MECHANICS DURING ANESTHESIA

Lung Volume

Resting lung volume (i.e., FRC), is reduced by almost 1 L by moving from upright to supine position; induction of anesthesia further decreases the FRC by approximately 0.5 L.[88] This reduces the FRC from approximately 3.5 to 2 L, a value close to RV. General anesthesia causes a fall in FRC (approximately 20%), whether breathing is controlled or spontaneous[89,90] and whether the anesthetic is inhalational or intravenous[91]; this is a major contributor to lowered oxygenation (discussed later). Muscle paralysis in the context of general anesthesia does not cause additional reduction in FRC.

The anatomic basis of the FRC reduction is not well understood. A landmark experiment on three volunteers using two-dimensional tomography suggested that a cephalad shift of the diaphragm, induced by anesthesia

and paralysis, was responsible.[92] Recent studies using CT scanning also suggest cephalad diaphragm shift, as well as a decrease in the transverse chest area.[91,93] However, other data suggest little role for the diaphragm, with possible caudal (not cephalad) shift of its anterior aspect.[94] Simple CT suggests a cranial displacement except in severe obstructive lung disease. Although the anatomic components of reduced FRC are debatable, the mechanism appears to be related to loss of respiratory muscle tone. FRC is maintained by a balance of the forces inward (lung recoil) versus forces outward (chest wall recoil, chest wall muscles, diaphragm). For example, maintenance of muscle tone using ketamine as the anesthetic does not reduce FRC.[91] Because patients are usually supine, the FRC will already have been reduced, and in elderly patients, this is particularly the case; in this context, the effects of anesthesia are more marked (see Fig. 19-9). As can be seen in the figure, FRC decreases with age assuming that weight does not change.

Compliance and Resistance of the Respiratory System

Static compliance of the total respiratory system (lungs and chest wall) is reduced on average from 95 to 60 mL/cm H_2O during anesthesia.[95] Most studies of lung compliance during anesthesia indicate a decrease compared with the awake state, and pooled data from several studies suggest that anesthesia is associated with a reduction in mean static compliance from almost 190 to approximately 150 mL/cm H_2O.[95] Data on changes in respiratory resistance are less clear. Although most studies suggest that anesthesia increases respiratory resistance, especially during mechanical ventilation,[95] no studies have corrected for lung volume and flow rates (both affect resistance considerably), and it is possible that changes in resistance occur merely because of volume (i.e., FRC) loss (Fig. 19-13).

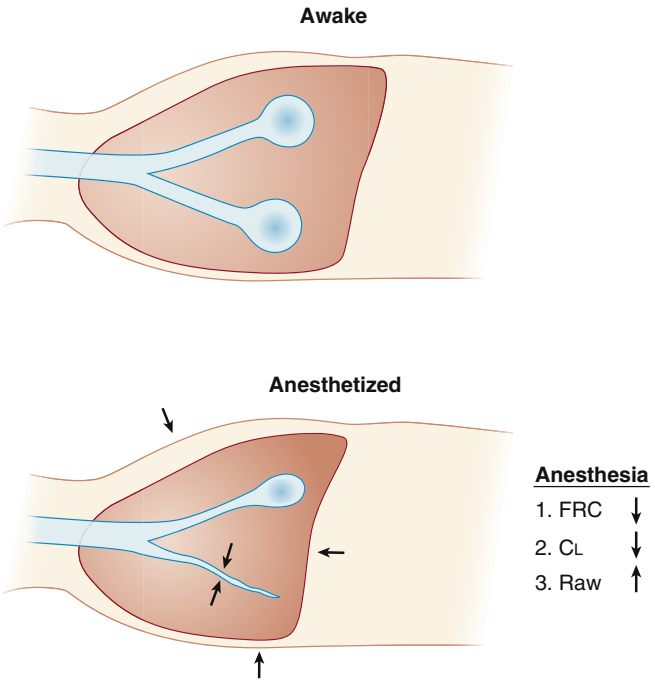


Figure 19-13. Anesthesia induces cranial shift of the diaphragm and a decrease of transverse diameter of the thorax. These effects contribute to a lowered functional residual capacity (FRC). The decreased ventilated volume (atelectasis and airway closure) can contribute to reduced compliance (C_L). Decreased airway dimensions by the lowered FRC can contribute to increased airway resistance (Raw).

ATELECTASIS AND AIRWAY CLOSURE DURING ANESTHESIA

The classic article by Bendixen and colleagues[96] proposed "a concept of atelectasis" as a cause of impaired oxygenation and reduced respiratory compliance during anesthesia.[96] That study described a progressive decrease in compliance that paralleled decreases in oxygenation in both anesthetized humans and experimental animals, which was interpreted as progressive of atelectasis. However, others noticed an abrupt decrease in compliance and PaO_2 during induction of anesthesia, and yet atelectasis could not be shown on conventional chest radiography.

Since then, CT scanning has improved our knowledge of the nature of anesthesia-induced atelectasis, and the technique reveals prompt development of densities in the dependent regions of both lungs during anesthesia (data up to 1990 reviewed by Moller and associates[86,97]). Morphologic studies of these densities in various animals supported the diagnosis of atelectasis. An example of atelectasis as seen on a CT scan is shown in Figure 19-14.

Atelectasis develops in approximately 90% of patients who are anesthetized, but it is unrelated to the choice of

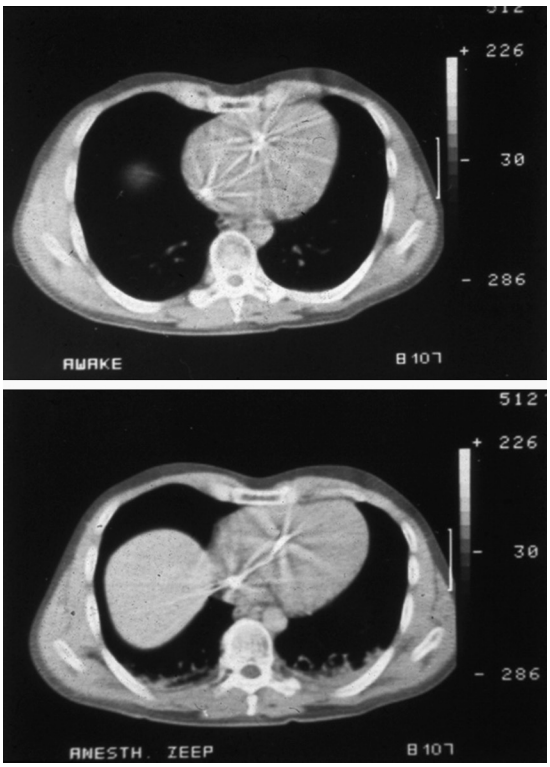


Figure 19-14. Computed tomography with transverse exposures of the chest when the subject is awake (upper panel) and anesthetized (lower panel). In the awake condition, the lung is well aerated (radiations from a pulmonary artery catheter are seen in the heart). During anesthesia, atelectasis has developed in the dependent regions (grey/white irregular areas). The large grey/white area in the middle of the right lung field is caused by a cranial shift of the diaphragm and the underlying liver.

anesthesia.[98] It is seen during spontaneous breathing and after muscle paralysis and when intravenous or inhaled anesthetics are used.[91] The atelectatic area near the diaphragm is 5% to 6% of the total lung area, but can easily exceed 20%. The amount of lung tissue that is collapsed is larger, because the atelectatic area consists mostly of lung tissue, whereas normal aerated lung consists of 20% to 40% tissue (the rest being air). Thus, 15% to 20% of the lung is atelectatic during uneventful anesthesia, before surgery has commenced; it decreases toward the apex, which usually remains aerated (Fig. 19-15). However, this degree of atelectasis is larger (upwards of 50% of lung volume) after thoracic surgery or cardiopulmonary bypass, and can last for several hours.[99] Abdominal surgery adds little to the atelectasis, but after such surgery it can persist for several days.[100]

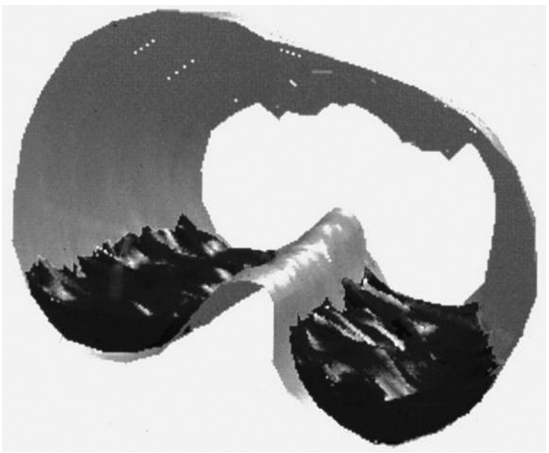


Figure 19-15. A three-dimensional reconstruction of the thorax of an anesthetized patient with atelectasis in the dependent regions of both lungs. There is a slight decrease in the degree of atelectasis toward the apex (distal in this image). *(Data from Reber A, Nylund U, Hedenstierna G: Position and shape of the diaphragm: implications for atelectasis formation.* Anaesthesia *53:1054-1061, 1998.)*

Atelectasis is an important cause of hypoxemia: there is a strong and significant correlation between the degree of atelectasis and the size of the pulmonary shunt (R = 0.81), where atelectasis is expressed as the percentage of lung area just above the diaphragm on CT scan and shunt is expressed as the percentage of cardiac output using the multiple inert gas elimination technique (MIGET).[98] The site of the increased shunt has been colocalized to the areas of atelectasis, using a technique that combines CT scanning and single photon emission computed tomography (SPECT; Fig. 19-16).[101] In addition to shunt, atelectasis may form a focus of infection and can certainly contribute to pulmonary complications.[102]

Aside from anesthesia (and the type of surgery), it is difficult to predict the development of atelectasis. The magnitude of atelectasis is often directly related to the BMI and inspired oxygen concentration.[89,91] Moreover, neither age[98] nor the presence of COPD[103] predicts the development or extent of atelectasis. In COPD, it may be that airway closure precedes (and therefore prevents) alveolar closure. Alternatively, the greater loss of lung (elastic recoil) versus chest wall tissue may serve to protect against atelectasis.

PREVENTION OF ATELECTASIS DURING ANESTHESIA

Several interventions can help prevent atelectasis[97] or even reopen collapsed tissue, as discussed in the following paragraphs.

Positive End-Expiratory Pressure

The application of PEEP (10 cm H_2O) has been repeatedly demonstrated to reexpand atelectasis partially

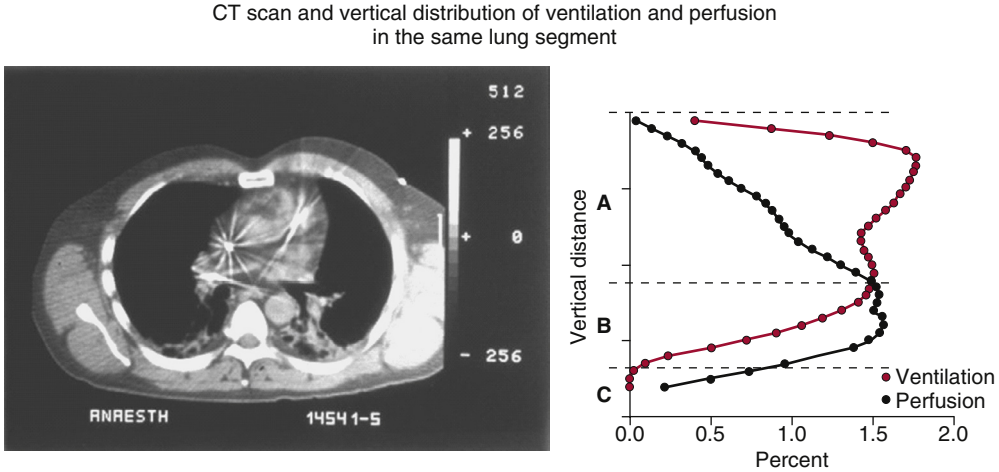


Figure 19-16. Atelectasis and distribution of ventilation and blood flow. The *left panel* is a cross-sectional slice of a computed tomographic image of the chest of an anesthetized patient, illustrating atelectasis in the basal (dorsal) regions. The *right panel* illustrates the distribution of ventilation and perfusion throughout that slice. The bulk of the ventilation is to the upper lung region (zone *A*), in contrast to the awake subject without atelectasis, and it exceeds the level of local perfusion; this results in wasted ventilation (i.e., deadspace) in the upper regions. In the lower region (zone *B*), the ventilation is less (probably because of intermittent airway closure) and is exceeded by the local perfusion, resulting in areas of low $\dot{V}_A/\dot{Q}$, causing hypoxemia. In the next lowest region (zone *C*), there is complete cessation of ventilation because of atelectasis, but some perfusion exists and causes a shunt. The farther from the top of the lung, the higher the perfusion; however, in the lowermost regions perfusion decreases (see text). *(Data from Hedenstierna G: Alveolar collapse and closure of airways: regular effects of anaesthesia,* Clin Physiol Funct Imaging *23:123-129, 2003.)*

(Fig. 19-17). Some atelectasis may persist and might require higher PEEP and inspiratory airway pressure.[91] The application of larger levels of PEEP can have complex effects. Reversal of hypoxemia is not proportionally associated with applied PEEP, and a threshold exists in many cases. In addition, SaO_2 may decrease during the application of increased PEEP for two reasons. First, the increased P_{PL} owing to the PEEP can impair venous return, especially in the presence of hypovolemia, lowering the cardiac output and DO_2 and thereby reducing mixed venous O_2 content ($C_{\bar{v}}O_2$). In the presence of an intrapulmonary shunt, such as with atelectasis, the mixed venous blood is shunted directly into pulmonary venous blood causing arterial desaturation. Second, increased PEEP can cause redistribution of blood flow away from the aerated, expanded regions (distended by PEEP) toward atelectatic areas (not distended by PEEP; Fig. 19-18).[104] In this context, persisting atelectasis in dependent lung receives a larger proportion of the total pulmonary blood flow than without PEEP.[59] Finally, anesthesia-induced atelectasis rapidly reemerges after discontinuation of PEEP.[91] Indeed, Hewlett and coworkers[105] in 1974 cautioned against "indiscriminate use of PEEP in routine anesthesia."

Recruitment Maneuvers

A sigh maneuver, or a large V_T, has been suggested for reversing atelectasis[10]; however, atelectasis is not uniformly reduced by a V_T increase or sigh up to P_{AW} of 20 cm H_2O.[106] Instead, a P_{AW} of 30 cm H_2O is required for initial opening, and 40 cm H_2O for more complete reversal (Fig. 19-19). In the presence of normal lungs, such inflation is equivalent to a VC and can therefore be called a *VC maneuver* (albeit achieved with positive P_{AW}). In addition, a significant hemodynamic effect is likely if the VC maneuver is sustained; in fact, inflation with a P_{AW} of 40 cm H_2O for 7 to 8 seconds appears to successfully open almost all anesthesia-induced atelectasis.[107]

Minimizing Gas Resorption

Although recruitment of anesthesia-induced atelectasis is completely possible with either PEEP or a VC maneuver, continuous application of some level of PEEP is required to prevent rapid recurrence of the atelectasis.[108] However, N_2—an insoluble gas that is not absorbed into the blood—can "splint" the alveolus if the alveolus is already opened. As a result, in anesthetized patients, a VC maneuver followed by ventilation with a gas mixture containing 60%

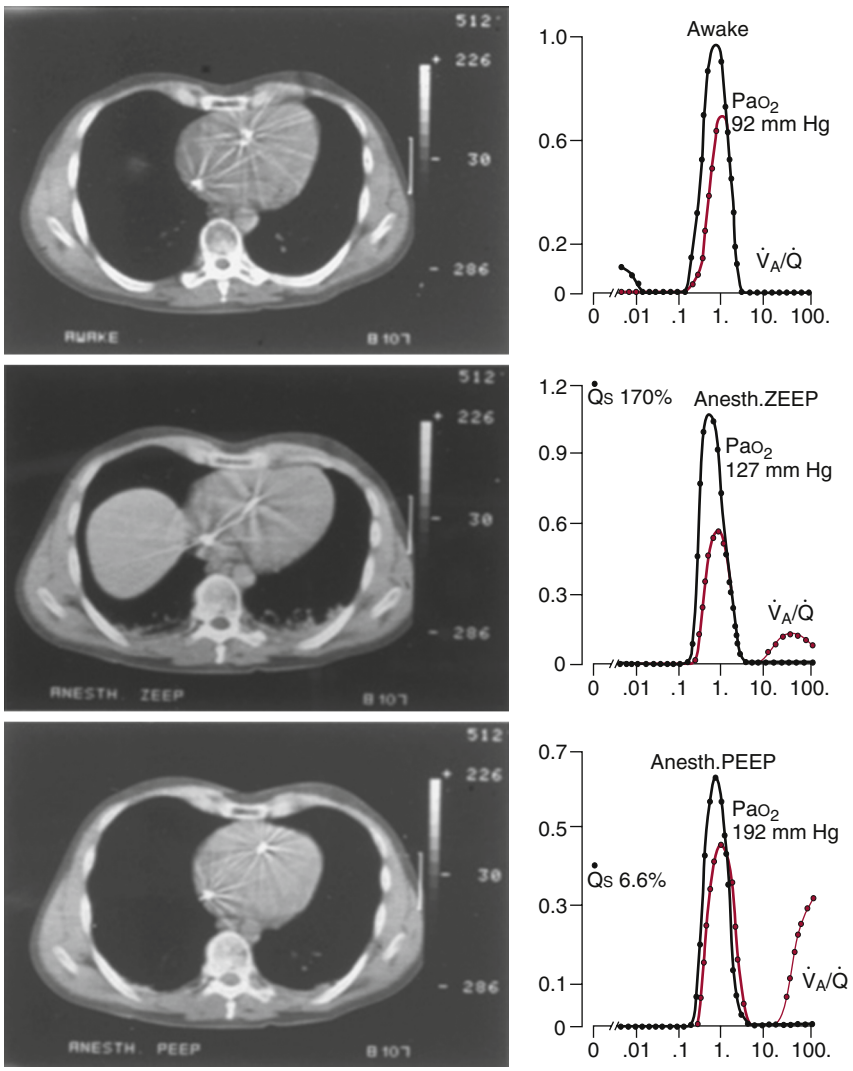


Figure 19-17. Computed tomographic scans and $\dot{V}_A/\dot{Q}$ distributions in the lung of a healthy, awake subject during anesthesia (zero positive end-expiratory pressure [ZEEP]) and during anesthesia (10 cm H_2O positive end-expiratory pressure [PEEP]). In the awake state, there is no atelectasis and the corresponding minor low $\dot{V}_A/\dot{Q}$ distribution (*left side* of plot) may reflect intermittent airway closure. During anesthesia with ZEEP, atelectasis is apparent in the lung bases (and the diaphragm has been pushed cranially). The low $\dot{V}_A/\dot{Q}$ has been replaced by atelectasis and large shunt; in addition, a small "high" $\dot{V}_A/\dot{Q}$ mode (right side of plot) may reflect alveolar dead space in upper lung regions. With the addition of PEEP during anesthesia, the collapsed lung tissue has been recruited and the shunt has been reduced considerably. Moreover, the "high" $\dot{V}_A/\dot{Q}$ mode (*right side* of plot) has significantly increased; this may reflect additional inflation of nonperfused upper lung.

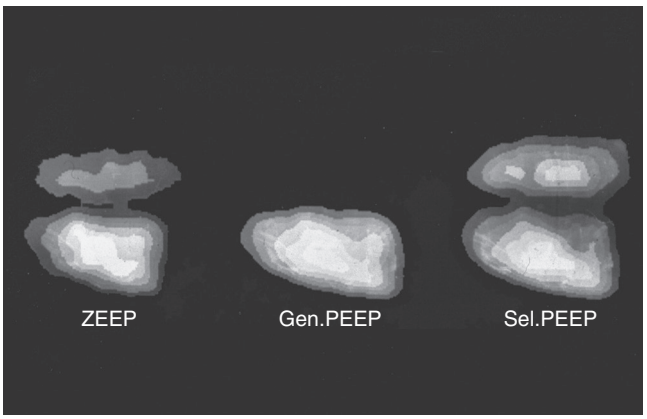


Figure 19-18. Gamma camera images of lung blood flow in an anesthetized subject in the lateral position. During mechanical ventilation with zero end-expiratory pressure (ZEEP), perfusion is predominantly (60% to 70% of cardiac output) to the lower lung. Applying PEEP (10 cm H_2O) to both lungs forces more perfusion to the lower lung, leaving almost no perfusion to the upper lung (i.e., major increase in V_D). In contrast, selective application of PEEP to the lower lung causes redistribution of perfusion to the upper lung. Of course, the image presented is perfused tissue (not total anatomic lung tissue; in the right lateral position the upper-right lung would be larger). *(From Hedenstierna G et al: Ventilation and perfusion of each lung during differential ventilation with selective PEEP,* Anesthesiology *61:369-376, 1984.)*

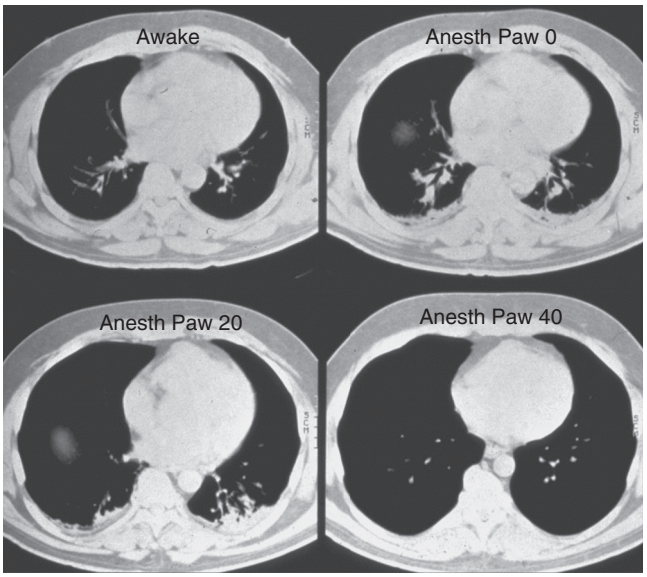


Figure 19-19. Computed tomographic (CT) scans during awake and anesthetized states with altered airway pressure (P_{AW}). The CT scan in the awake subject (*upper left panel*) shows normal vasculature and no atelectasis. During anesthesia (P_{AW}, 0 cm H_2O; *upper right panel*), bilateral basal atelectasis is seen; the PAW is increased in increments (20 cm H_2O shown), but the atelectasis is not reversed until a P_{AW} of 40 cm H_2O is applied (*lower right panel*). Thus, a vital capacity maneuver was required to open the lung. *(From Rothen HU et al: Re-expansion of atelectasis during general anaesthesia: a computed tomography study,* Br J Anaesth *71:788-795, 1993.)*

N_2 (40% O_2) reduced the propensity for reaccumulation of atelectasis with only 20% reappearing 40 minutes after recruitment.[108]

The same principles apply in the practice of preoxygenation of patients during induction of anesthesia.

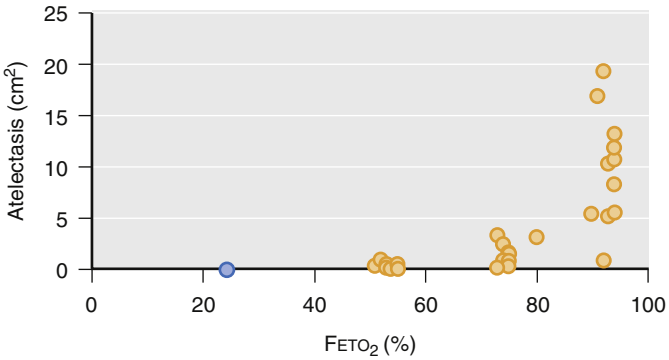


Figure 19-20. Atelectasis formation in anesthetized subjects following preoxygenation with different inspired oxygen concentrations. Increasing the Fio_2 during preoxygenation increases the propensity to subsequent atelectasis (closed symbols), although there is much variability. The open circle at around an expired oxygen concentration (FeO_2) of 25% represents data from anesthesia being induced while breathing 30% O_2. *(From Rothen HU et al: Prevention of atelectasis during general anaesthesia,* Lancet *345:1387-1391, 1995.)*

Here, the aim is to prevent O_2 desaturation (i.e., gain an O_2 safety margin) during induction before the airway has been secured when the anesthesiologist can better manage ventilation and oxygenation. Traditionally, the application of Fio_2 1.0 has been used. Although the SaO_2 is usually well maintained with this approach, atelectasis inevitably forms. The use of 30% versus 100% O_2 during induction was demonstrated in a clinical study to eliminate the formation of atelectasis.[109] Later, a comparison of breathing 100%, 80%, and 60% O_2 during induction demonstrated ubiquitous atelectasis with 100%, less with 80%, and even less with 60% O_2 (Fig. 19-20); however, the trade-off for less atelectasis was a shorter safety margin before occurrence of O_2 desaturation.[110]

An alternative approach may be continuous positive airway pressure (CPAP). Application of CPAP 10 cm H_2O permitted the use of 100% inspired O_2 without formation of significant degrees of atelectasis.[111] This might provide an ideal combination of minimal risk of either O_2 desaturation or atelectasis, but it has not been repeatedly verified.

Maintenance of Muscle Tone

Because loss of muscle tone in the diaphragm or chest wall appears to increase the risk of atelectasis, techniques that preserve muscle tone may have advantages. Intravenous ketamine does not impair muscle tone and is the only individual anesthetic that does not cause atelectasis. If neuromuscular blockade is added, atelectasis occurs as with other anesthetics.[91] Ketamine is an extremely useful agent in special circumstances, but it has significant challenges in routine cases.

An experimental approach is restoration of respiratory muscle tone by diaphragm pacing. This approach is achieved with phrenic nerve stimulation, and it can modestly reduce the degree of atelectasis; however, the effect is minor and the approach complicated.[112]

Atelectasis Following Surgery

Hypoxemia is common after anesthesia and surgery. It is enhanced by breathing oxygen before induction of

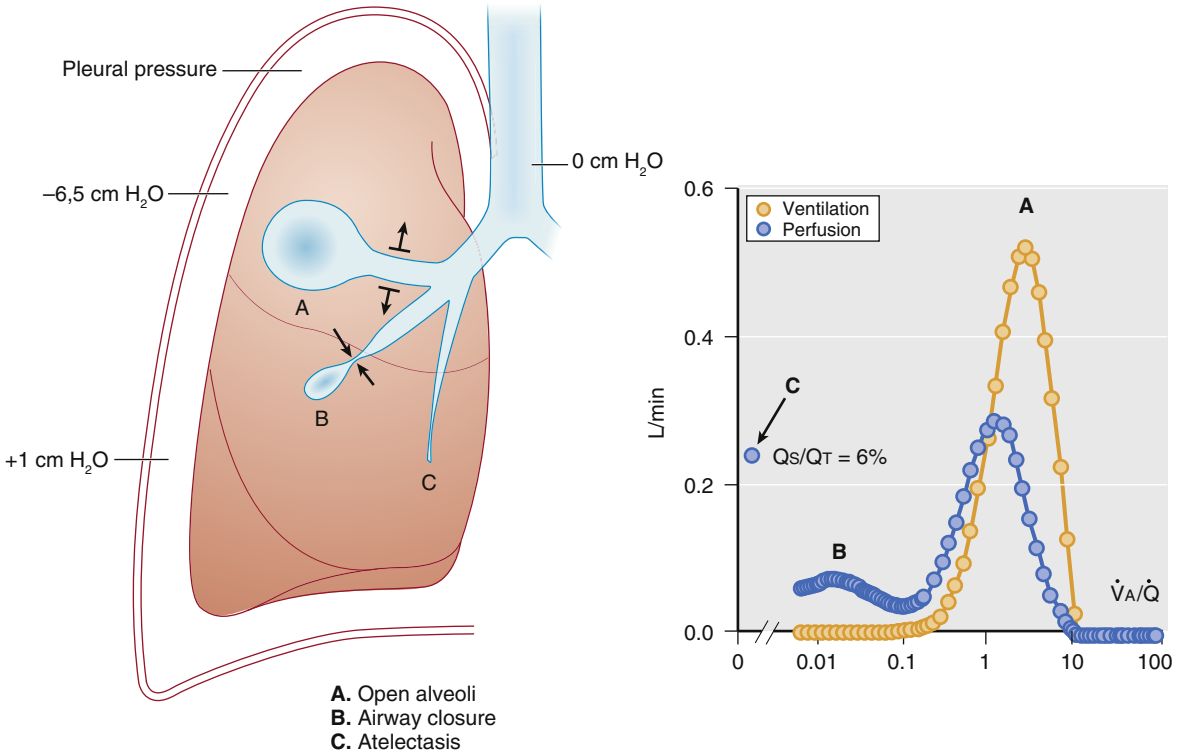


Figure 19-21. A three-compartment model of ventilation and perfusion during anesthesia. In the upper regions, the alveoli and airways are open (*left panel, A*). In the middle region, the airways are intermittently closed (*B*), and atelectasis is present in the lower region (*C*). The corresponding ventilation-perfusion distribution (multiple inert gas elimination technique) is illustrated in the *right panel*. Mode *A* reflects good ventilation and perfusion, whereas mode *B* reflects intermittent airway closure. In addition, there is a shunt in the atelectatic region (mode *C*).

anesthesia and suctioning of the airway (negative pressure) before extubation of the trachea. In addition, splinting and inhibition of coughing associated with pain can cause atelectasis postoperatively. Several approaches have been tried to address such atelectasis-associated hypoxemia following surgery. Administration of 100% O_2 coupled with a VC maneuver is not effective; this is probably because while the VC maneuver recruits lung, alveolar opening is not maintained (in fact closure is encouraged by the N_2-free O_2).[113] However, a VC maneuver followed by a lower O_2 concentration (40% O_2 in N_2) can maintain an open lung until the end of anesthesia.[107] Oxygenation is sustained for a longer period following ventilation with 50% O_2 in air (i.e., N_2) compared with 100%, following cardiopulmonary bypass.[114] Finally, treatment of postoperative hypoxemia, considered to be due to atelectasis, is associated with better outcomes when CPAP is used instead of 100% O_2.[115]

AIRWAY CLOSURE

Intermittent airway closure reduces ventilation of the affected alveoli. Such lung regions can become regions of low $\dot{V}_A/\dot{Q}$ if perfusion is maintained or is not reduced to the same degree as ventilation. The propensity to airway closure increases with age[49] (see Fig. 19-9), as does perfusion to low $\dot{V}_A/\dot{Q}$ regions.[116] Anesthesia reduces FRC by about 0.5 L,[88] which increases airway closure during tidal ventilation.[117,118] In fact, the reduction in ventilation in the nonatelectatic lung (Fig. 19-21) is caused by airway closure. In addition, ventilation in these regions is less than perfusion (i.e., regions of low $\dot{V}_A/\dot{Q}$) and contributes to impaired oxygenation during anesthesia. Taken together, the combination of atelectasis and airway closure explain about 75% of the overall impairment in oxygenation.[89] In addition, where (CV – ERV) indicates the amount of airway closure occurring above FRC (and ERV is expiratory reserve volume), this value increased with induction of anesthesia, and there is good correlation between low $\dot{V}_A/\dot{Q}$ and the extent of airway closure.[89] In summary, a simple three-compartment lung model (normal $\dot{V}_A/\dot{Q}$ matching regions, region of airway closure, and atelectatic lung) describes well the components contributing to impairment of oxygenation during anesthesia (see Fig. 19-21).

DISTRIBUTION OF VENTILATION AND BLOOD FLOW DURING ANESTHESIA

Distribution of Ventilation

Redistribution of inspired gas away from dependent to nondependent lung regions has been demonstrated, using isotope techniques in anesthetized supine humans. Radiolabeled aerosol and SPECT demonstrate that ventilation is distributed mainly to the upper lung regions, with a successive decrease toward the lower lung regions, and an absence of ventilation in the lowermost regions, a finding consistent with the atelectasis demonstrable using CT (see Fig. 19-16).[101]

Recruitment maneuvers increase dependent lung ventilation in anesthetized subjects in the lateral[119] and supine[120] positions, restoring the distribution of ventilation to that in the awake state. Thus, restoration of overall FRC toward the awake level returns gas distribution toward the awake pattern. The explanations are recruitment of atelectatic lung, reopening of closed airways, and further expansion of already expanded (upper) lung regions, decreasing regional compliance and lessening incremental ventilation.

Distribution of Lung Blood Flow

The distribution of lung blood flow has been studied by injection of radioactively labeled macroaggregated albumin and SPECT.[101] During anesthesia, a successive increase in perfusion occurs from upper towards lower regions, with a slight drop in perfusion in the lowermost portion of the lung, which was atelectatic on simultaneous CT (see Fig. 19-16). PEEP will impede venous return to the right heart and reduce cardiac output. It can also affect pulmonary vascular resistance, although this would have little effect on cardiac output. In addition, PEEP redistributes blood flow toward dependent lung regions,[59,120] reducing flow (and increasing deadspace) in the upper lung; the increased dependent flow may increase shunt through atelectatic lung.[104]

HYPOXIC PULMONARY VASOCONSTRICTION

Several inhaled—but not intravenous—anesthetics inhibit HPV in isolated lung preparations.[121] Human studies of HPV are complex with multiple parameters changing simultaneously, thereby confounding the HPV response with changes in cardiac output, myocardial contractility, vascular tone, blood volume distribution, pH, P_{CO_2}, and lung mechanics. However, studies with no obvious changes in cardiac output, isoflurane and halothane depress the HPV response by 50% at a minimum alveolar concentration (MAC) of 2 (Fig. 19-22).[122]

VENTILATION-PERFUSION MATCHING DURING ANESTHESIA

DEAD SPACE, SHUNT, AND VENTILATION-PERFUSION RELATIONSHIPS

CO_2 Elimination

Anesthesia impairs CO_2 elimination and oxygenation of blood. The explanation for reduced CO_2 elimination is reduced minute ventilation ($\dot{V}_E$) because of respiratory depression, or where this is preserved, because of an increase in the V_D/V_T. Single-breath washout recordings demonstrate that "anatomic" dead space is unchanged, indicating that increased V_D/V_T is alveolar and confirmed by MIGET scan (Fig. 19-23).[10] Such high $\dot{V}_A/\dot{Q}$ can be explained by the tiny perfusion of corner vessels in interalveolar septa in the upper lung regions, where alveolar pressure can exceed pulmonary vascular pressure (zone I).[85] The impaired CO_2 elimination is most easily corrected by increasing the ventilation and is seldom a problem in routine anesthesia with mechanical ventilation.

Oxygenation

The impairment in arterial oxygenation during anesthesia is more marked with increased age, obesity, and smoking (see Chapter 80).[123,124] Venous admixture, as calculated by the standard oxygen shunt equation, is also increased during anesthesia to approximately 10% of cardiac output. However, this is an averaged calculation that considers hypoxia caused by pure shunt only, when actually it is due to a combination of "true" shunt (i.e., perfusion of nonventilated lung), poor ventilation of some regions, and regions that are ventilated but are perfused in excess of their ventilation (low $\dot{V}_A/\dot{Q}$ regions). The combination of these effects is called *venous admixture*. The shunt equation (derived in Box 19-2) assumes that all blood flow through the lung goes to either of two compartments: in one (the non–shunt fraction), all the blood is oxygenated; and in the other (the shunt fraction), all blood is shunted.

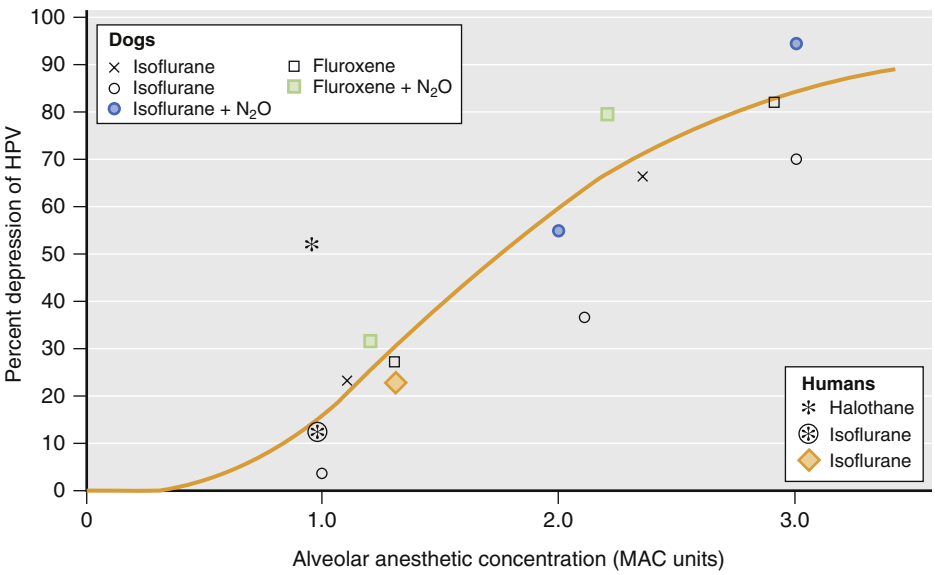


Figure 19-22. Effect of inhaled anesthetics on hypoxic pulmonary vasoconstriction (HPV). A concentration of 1 MAC causes a 20% to 30% depression of HPV, and the HPV depression decreases sharply with higher concentrations. The effect is that the shunt (i.e., perfusion through nonventilated regions) will be less reduced during inhalational anesthesia. *(From Marshall BE: Hypoxic pulmonary vasoconstriction,* Acta Anaesthesiol Scand Suppl *94:37-41, 1990.)*

The shunt equation (or venous admixture) can be written[125]:

$$\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{(C_cO_2 - C_aO_2)}{(C_cO_2 - C_{\bar{v}}O_2)}$$

Because pulmonary end-capillary blood is assumed to be maximally saturated (therefore, $S_cO_2 = 1$), the quantity of dissolved O_2 can be ignored, and it can be the difference between $C_{\bar{v}}O_2$ and $C_{\bar{v}}O_2$ can be assumed to be small ($C_vO_2 = C_{\dot{v}}O_2$):

$$\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{(1 - S_aO_2)}{(1 - S_vO_2)}$$

Thus, the effect of interventions on estimated shunt can be calculated easily from the changes in SaO_2 and SvO_2.

The extent of venous admixture depends on the inspired oxygen fraction (Fio_2). The higher the inspired oxygen fraction, the less there are of the low $\dot{V}_A/\dot{Q}$ regions. However, with high Fio_2, regions with low $\dot{V}_A/\dot{Q}$ may collapse because of gas adsorption and be transformed to shunt regions.[126] A good correlation between venous admixture vs. the sum of "true" shunt and perfusion of low $\dot{V}_A/\dot{Q}$ regions was seen in a study involving 45 anesthetized subjects (Fig. 19-24).[98] Derivation of the "oxygen shunt" or venous admixture is shown in Box 19-2.

In young healthy volunteers during anesthesia with thiopental and methoxyflurane, both ventilation and perfusion were distributed to wider ranges of $\dot{V}_A/\dot{Q}$ ratios,

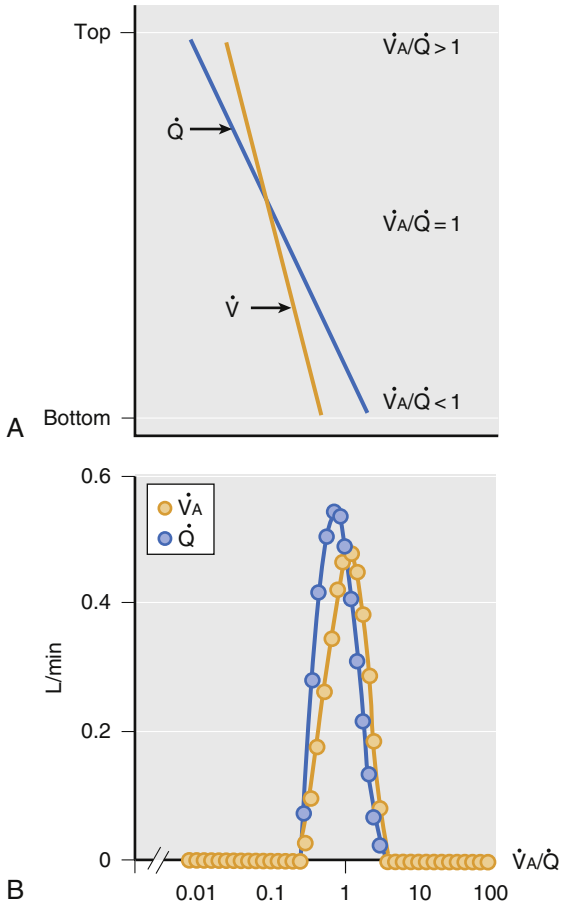


Figure 19-23. A schematic drawing of **(A)** the vertical distributions of ventilation ($\dot{V}_A$) and blood flow through the lung ($\dot{Q}$) and **(B)** the resulting ventilation-perfusion distribution ($\dot{V}_A/\dot{Q}$). The $\dot{V}_A/\dot{Q}$ distribution is centred at a ratio of 1, corresponding to the intersection of the ventilation and perfusion distribution curves. The slightly larger ventilation than perfusion in upper lung regions contribute to the high $\dot{V}_A/\dot{Q}$ ratios greater than 1, whereas the larger perfusion than ventilation in the lower part of the lung is the cause of the lower $\dot{V}_A/\dot{Q}$ ratios, less than 1. Although there is a moderate increase in ventilation down the lung, the increase in perfusion is greater.

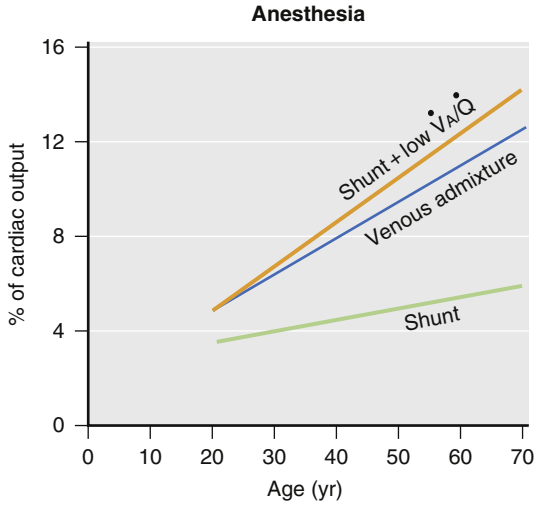


Figure 19-24. The effect of age on oxygenation during anesthesia. The combination of shunt with low $\dot{V}_A/\dot{Q}$ increases sharply with age (as does the degree of venous admixture). The increase in shunt with age, while significant, is less striking. *(From Gunnarsson L et al: Influence of age on atelectasis formation and gas exchange impairment during general anaesthesia,* Br J Anaesth *66:423-432, 1991.)*

BOX 19-2 *Derivation of the Venous Admixture (Shunt) Equation*

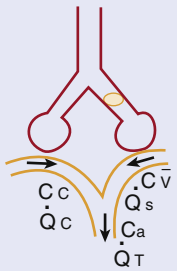
$$Ca \times \dot{Q}T = \left(Cc' \times \dot{Q}C\right) + \left(C\bar{v} \times \dot{Q}S\right) \quad (1)$$

$$\dot{Q}C = \dot{Q}T - \dot{Q}S \quad (2)$$

By inserting Equation 2 (accounts for all blood flow through the lungs) into Equation 1 (accounts for all oxygen carriage through the lungs),

$$Ca \times \dot{Q}T = \left(Cc \times \left[\dot{Q}T - \dot{Q}S\right]\right) + (C\bar{v} \times \dot{Q}S)$$

Rearranging,



$$\frac{\dot{Q}S}{\dot{Q}T} = \frac{Cc' - Ca}{Cc' - C\bar{v}}$$

where Cc', Ca, and Cv are oxygen content in pulmonary end-capillary, arterial, and mixed venous blood, respectively; $\dot{Q}T$ is cardiac output; $\dot{Q}c$ is capillary flow; and $\dot{Q}s$ is shunt.

which can be expressed as an increase in the logarithmic standard deviation of the perfusion distribution (log SD$\dot{Q}$). In a similar group of patients studied during halothane anesthesia and muscle paralysis, log SD$\dot{Q}$ was almost doubled (0.43 awake, 0.80 during anesthesia). In addition, true shunt was increased to a mean of 8%. A similar increase in shunt from 1% awake to a mean of 9% during anesthesia was recorded in a study on middle-aged (37 to 64 years) surgical patients, and there was a widening of the distribution (log SD$\dot{Q}$: 0.47 awake, 1.01 during anesthesia). In older patients with more severe impairment of lung function, halothane anesthesia with muscle paralysis, with or without nitrous oxide, caused considerable widening of the $\dot{V}_A/\dot{Q}$ distribution (log SD$\dot{Q}$ 0.87 awake, 1.73 during anesthesia). In addition, shunt increased to a mean of 15%, with large variation among patients (0% to 30%). Thus, the most consistent findings during anesthesia are an increased $\dot{V}_A/\dot{Q}$ mismatch, expressed as an increased log SDQ, and an increase in shunt. For review, see the article by Hedenstierna.[85]

Spontaneous ventilation is frequently reduced during anesthesia; therefore, inhaled anesthetics[127] or barbiturates[128] reduce sensitivity to CO_2. The response is dose-dependent; ventilation decreases with deepening anesthesia. Anesthesia also reduces the response to hypoxia, possibly because of effects on the carotid body chemoreceptors.[129]

The effects of anesthesia on respiratory muscle function are becoming better understood.[130] The effects are not uniform. Rib cage excursions diminish with deepening anesthesia.[131] The normal ventilatory response to CO_2 is produced by the intercostal muscles,[132,133] but with no clear increase in rib cage motion with CO_2 rebreathing during halothane anesthesia. Thus, the reduced ventilatory response to CO_2 during anesthesia is due to impeded function of the intercostal muscles.

FACTORS THAT INFLUENCE RESPIRATORY FUNCTION DURING ANESTHESIA

SPONTANEOUS BREATHING

Most studies of lung function have been performed on anesthetized, mechanically ventilated subjects or animals. Spontaneous breathing has been studied rarely. FRC decreases to the same extent during anesthesia, regardless of whether a muscle relaxant is used,[90,91] and atelectasis occurs to almost the same extent in anesthetized, spontaneously breathing subjects as during muscle paralysis.[134] Furthermore, the cranial shift of the diaphragm, as reported by Froese and Bryan,[92] was of the same magnitude both during general anesthesia with spontaneous breathing and with muscle paralysis, even though a difference in movement of the diaphragm from the resting position was noted. Thus, during spontaneous breathing, the lower, dependent portion of the diaphragm moved the most, whereas with muscle paralysis, the upper, nondependent part showed the largest displacement.

All these findings have raised the question of whether regional ventilation is different between spontaneous breathing and mechanical ventilation and whether mechanical ventilation worsens $\dot{V}_A/\dot{Q}$ as a consequence of poor ventilation of well-perfused, dependent lung regions. However, there is not much support for worsening of gas exchange by muscle paralysis in the literature. There is also no support from the few studies of $\dot{V}_A/\dot{Q}$ distribution that have been performed. Dueck and colleagues[135] found the same increase in $\dot{V}_A/\dot{Q}$ mismatch in anesthetized sheep during anesthesia, regardless of whether they were spontaneously breathing or ventilated mechanically. The log SDQ, indicating the degree of mismatch, increased (0.66 [awake], 0.83 [inhaled anesthesia with spontaneous breathing], 0.89 [mechanical ventilation]). Shunt is also increased during anesthesia from 1% (awake) to 11% (anesthetized, spontaneous breathing) or 14% (anesthetized, mechanical ventilation). In a study of anesthetized human subjects, shunt and log SDQ increased from 1% and 0.47 while awake to 6% and 1.03 during anesthesia with spontaneous breathing and 8% and to 1.01 during mechanical ventilation.[85] Thus, most of the gas exchange effects of anesthesia occurs during spontaneous breathing, with little or no further derangement added by muscle paralysis and mechanical ventilation.

INCREASED OXYGEN FRACTION

In the studies cited thus far, an inspired oxygen fraction (Fio_2) of approximately 0.4 was used. Anjou-Lindskog and colleagues[136] induced anesthesia in subjects breathing air (Fio_2, 0.21) in middle-aged to older patients during intravenous anesthesia before elective lung surgery and found only small shunts of 1% to 2%, although log SDQ increased from 0.77 to 1.13. When Fio_2 was increased to 0.5, the shunt increased (by 3% to 4%). In another study of older patients during halothane anesthesia,[85] an increase in Fio_2 from 0.53 to 0.85 caused an increase in shunt from 7% to 10% of cardiac output. Thus, increasing Fio_2 increases shunt, possibly because of attenuation of HPV by increasing Fio_2[122] or further development of atelectasis and shunt in lung units with low $\dot{V}_A/\dot{Q}$ ratios.[126]

BODY POSITION

Functional residual capacity is reduced dramatically by the combined effect of the supine position and anesthesia (see Chapter 41). The effects on the FRC of inducing anesthesia in the upright position were tested by Heneghan and associates,[137] and there was no difference in oxygenation in the semirecumbent versus supine position. Decreased cardiac output and enhanced inhomogeneity of blood flow distribution can outweigh any effects of posture. Fractional perfusion of the most dependent lung regions—likely poorly or not ventilated—may actually have been increased in the semirecumbent position. In the lateral position, differences in lung mechanics, resting lung volumes, and atelectasis formation between the dependent and nondependent portions of the lung have been demonstrated[138] and shown to result in further disturbance of the ventilation-perfusion match, with severe impairment in oxygenation. However, there are large and unpredictable inter-individual variations.[139] Using isotope techniques, an increase in $\dot{V}_A/\dot{Q}$ mismatch was also demonstrated in anesthetized, paralyzed patients in the lateral position,[140] and an improvement was noticed in

the prone position.[141] In addition, the vertical inhomogeneity of perfusion distribution is less marked in the prone position,[69] possibly reflecting regional differences in vascular configuration that promote perfusion of dorsal lung regions, regardless of whether they are in a dependent or nondependent position. Finally, distribution of ventilation may be uniform in anesthetized subjects when prone.[142]

AGE

Oxygenation is less efficient in older patients (see Chapter 80).[10] However, the formation of atelectasis does not increase with age in adults, and the few CT studies of infants during anesthesia suggest greater degrees of atelectasis.[98] In addition, shunt is independent of age between 23 and 69 years. However, $\dot{V}_A/\dot{Q}$ mismatch increases with age, with enhanced perfusion of low $\dot{V}_A/\dot{Q}$ regions when awake and when anesthetized. The major cause of impaired gas exchange during anesthesia in those younger than 50 years is shunt, whereas beyond 50 years $\dot{V}_A/\dot{Q}$ mismatch (i.e., increased log SDQ) becomes increasingly important (see Fig. 19-24). Because the correlation between log SDQ and age during anesthesia is almost parallel with that during the awake state, it can be said that anesthesia worsens $\dot{V}_A/\dot{Q}$ matching to the same extent as 20 years of aging.

OBESITY

Obesity worsens oxygenation (see Chapter 71)[143,144] predominantly because of reduced FRC resulting in a greater propensity to airway closure.[145] In addition, the use of high inspired oxygen concentrations promotes rapid atelectasis formation in alveoli distal to closed airways,[89,110] and the atelectasis seems to be larger than in normal weight subjects (Fig. 19-25).[145,146]

Preventing a decrease in FRC by applying CPAP during induction of anesthesia probably reduces atelectasis formation, and thereby maintains oxygenation.[124,147,148] Indeed, the reduced "safety window" (the time taken to develop desaturation following breathing oxygen before induction of anesthesia) is much reduced in obese patients, and this may be prolonged by PEEP or CPAP[149] increasing lung volume and increasing the reservoir of O_2 available for diffusion into the capillary blood.

The use of high levels of inspired oxygen concentration, often almost 100%, to keep an acceptable level of oxygenation during anesthesia and surgery may be the simplest but not necessarily the best approach. It will promote further atelectasis formation,[109] and if the shunt is larger than 30%, which may well be the case in these patients, additional oxygen will add little to arterial oxygenation.[150] The application of PEEP has been advocated, and it may reduce the atelectasis[123,145,147] but will also have adverse effects, such as reduced cardiac output and redistribution of blood flow toward residual collapsed lung regions. Ventilation with inflations close to VC to reopen collapsed tissue, followed by ventilation with added PEEP, is another option. Recruitment of the lung with an inflation to 55 cm H_2O opened essentially all collapsed lung tissue in patients with a BMI of

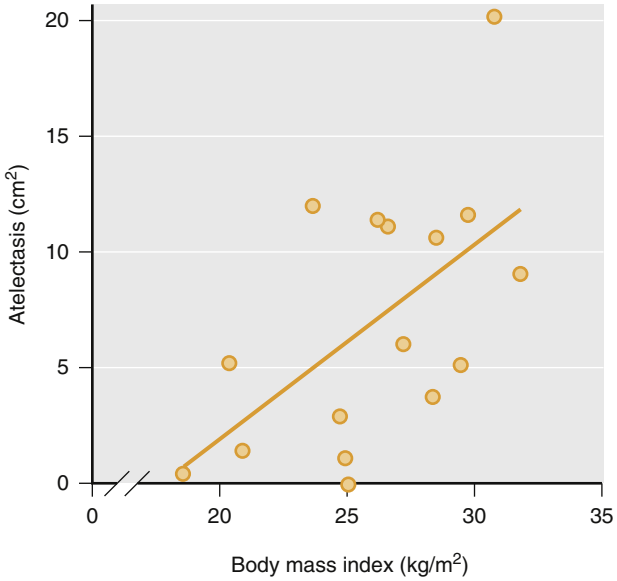


Figure 19-25. Relationship between body mass index (BMI) and extent of atelectasis during general anesthesia. As BMI increases, so does the extent of atelectasis (although there is considerable variability). *(From Rothen HU et al: Re-expansion of atelectasis during general anaesthesia: a computed tomography study,* Br J Anaesth *71:788-795, 1993.)*

40 kg/m² or more.[151] However, a recruitment alone did not keep the lung open for more than a few minutes. To keep the lung open, a PEEP of 10 cm H_2O after the recruitment was needed. PEEP of 10 was not enough to open up the lung.[151] Body position can have a substantial effect on lung volume and should be considered to the extent that surgery allows.[152]

PREEXISTING LUNG DISEASE

Smokers and patients with chronic lung disease have impaired gas exchange in the awake state, and anesthesia-associated deterioration in oxygenation is greater than in healthy individuals.[10] Interestingly, smokers with moderate airflow limitation may have less shunt as measured by MIGET than in subjects with healthy lungs. Thus, in patients with mild to moderate bronchitis who were to undergo lung surgery or vascular reconstructive surgery in the leg, only a small shunt was noticed, but log SDQ was increased.[85] In patients with chronic bronchitis studied by MIGET and CT, no or limited atelectasis developed during anesthesia and no or only minor shunt[103]; however, a considerable mismatch was seen with a large perfusion fraction to low $\dot{V}_A/\dot{Q}$ regions. Consequently, arterial oxygenation was more impaired than in lung-healthy subjects, but the cause was different from that in healthy subjects. A possible reason for the absence of atelectasis and shunt in these patients is chronic hyperinflation, which changes the mechanical behavior of the lungs and their interaction with the chest wall such that the tendency to collapse is reduced. It should be kept in mind that a patient with obstructive lung disease may have large regions with low $\dot{V}_A/\dot{Q}$ ratios that can be converted over time to resorption atelectasis. Thus, the protection against atelectasis formation during anesthesia by

TABLE 19-1 CAUSES OF HYPOXEMIA

Disturbance	Pao_2 (Breathing Air) at Rest	Pao_2 (Breathing Oxygen) at Rest	Pao_2 (Breathing air) With Exercise (Versus Rest)	$Paco_2$
Hypoventilation	Reduced	Normal	No change or further decrease	Increased
$\dot{V}_A/\dot{Q}$ mismatch	Reduced	Normal	No change or minor increase or decrease	Normal
Shunt	Reduced	Reduced	No change or further decrease	Normal
Diffusion impairment	Reduced	Normal	Small to large decrease	Normal

the obstructive lung disease might not last long. Regions with low $\dot{V}_A/\dot{Q}$ can be replaced by atelectasis as a result of slow absorption of gas behind occluded airways later during surgery and in the postoperative period.

REGIONAL ANESTHESIA

The ventilatory effects of regional anesthesia depend on the type and extension of motor blockade (see Chapters 56 and 57). With extensive blocks that include all the thoracic and lumbar segments, inspiratory capacity is reduced by 20% and expiratory reserve volume approaches zero.[153,154] Diaphragmatic function, however, is often spared, even in cases of inadvertent extension of subarachnoid or epidural sensory block up to the cervical segments.[153] Skillfully handled regional anesthesia affects pulmonary gas exchange only minimally. Arterial oxygenation and carbon dioxide elimination are well maintained during spinal and epidural anesthesia. This is in line with the findings of an unchanged relationship of CC and FRC[155] and unaltered distributions of ventilation-perfusion ratios assessed by MIGET during epidural anesthesia.[85]

CAUSES OF HYPOXEMIA AND HYPERCAPNIA

In the previous sections, we discussed ventilation, gas distribution, and the respiratory mechanics that govern distribution, diffusion, and pulmonary perfusion. All these components of lung function can affect the oxygenation of blood, and all except diffusion can also measurably affect CO_2 elimination. The different mechanisms behind hypoxemia and CO_2 retention, or hypercapnia or hypercarbia, have been mentioned previously but will be analyzed in more detail here.

Causes of hypoxemia include hypoventilation, $\dot{V}_A/\dot{Q}$ mismatch, impaired diffusion, and right-to-left shunt (Table 19-1). Hypercapnia is usually caused by hypoventilation although it can be caused by, $\dot{V}_A/\dot{Q}$ mismatch and shunt (Table 19-2). Increased $\dot{V}CO_2$ occurs in hypermetabolic conditions (e.g., fever, malignant hyperthermia, thyroid crisis) or with the use of CO_2-generating buffers such as $NaHCO_3$.

HYPOVENTILATION

If ventilation is low in proportion to metabolic demand, elimination of CO_2 will be inadequate, and CO_2 will accumulate in the alveoli, blood, and other body tissues. Hypoventilation is often defined as ventilation that results in a $Paco_2$ greater than 45 mm Hg (6 kPa). Thus, hypoventilation could be present even when minute ventilation is high, provided the metabolic demand or dead space ventilation is increased to a greater extent.

TABLE 19-2 MECHANISMS OF HYPOXEMIA IN DIFFERENT LUNG DISORDERS

Disorder	Hypoventilation	Diffusion Impairment	$\dot{V}_A/\dot{Q}$ Mismatch	Shunt
Chronic bronchitis	(+)	–	++	–
Emphysema	+	++	+++	–
Asthma	–	–	++	–
Fibrosis	–	++	+	+
Pneumonia	–	–	+	++
Atelectasis	–	–	–	++
Pulmonary edema	–	+	+	++
Pulmonary emboli	–	–	++	+
Acute respiratory distress syndrome	–	–	+	+++

The increased alveolar P_{CO_2} reduces the alveolar space available for oxygen. Alveolar PO_2 (PAO_2) can be estimated by the alveolar gas equation (see Box 19-1). The simplified equation is expressed:

$$PaO_2 = P_IO_2 - \left(Pa_{CO_2}/R\right)$$

Assuming that the respiratory exchange ratio (R) is 0.8 (more or less true at rest), PAO_2 can be estimated. In the ideal lung, PaO_2 equals PAO_2. For example, if PiO_2 is 149 mm Hg (19.9 kPa) and $Paco_2$ is 40 mm Hg (5.3 kPa), then PaO_2 is 99 mm Hg (13.2 kPa). If hypoventilation develops and the $Paco_2$ rises to 60 mm Hg (8 kPa) and there is no other gas exchange impairment, the PaO_2 will fall to 74 mm Hg (9.9 kPa). Clearly, a decrease in PaO_2 caused by hypoventilation is easily overcome by increasing PiO_2 (i.e., by increasing Fio_2). If there is a gap between the PAO_2 (estimated from this equation) and the measured (actual) PaO_2, then a cause of hypoxemia in addition to hypoventilation is present. These causes are discussed in the following paragraphs.

VENTILATION-PERFUSION MISMATCH

For optimal gas exchange, ventilation and perfusion must match each other in all lung regions. At rest, both ventilation and perfusion increase downward through the lung. However, perfusion increases more than ventilation, the

TABLE 19-3 MEAN (SD) VENTILATION-PERFUSION RELATIONSHIPS WITH NO CARDIOPULMONARY DISEASE (NORMAL, *N* = 45), AWAKE AND DURING GENERAL ANESTHESIA AND MUSCLE PARALYSIS

	$\dot{Q}$ mean	log SD$\dot{Q}$	$\dot{V}$ Mean	Log SD$\dot{V}$	Shunt (% Q_T)	Dead Space (% V_T)	Pao_2/Fio_2 (kPa)*
Awake	0.76 (0-33)	0.68 (0.28)	1.11 (0.52)	0.52 (0.15)	0.5 (1.0)	34.8 (14.2)	59.5 (8.1)
Anesthetized	0.65 (0.34)	1.04 (0.36)	1.38 (0.76)	0.76 (0.31)	4.8 (4.1)	35.0 (9.9)	50.9 (15.2)

log SD$\dot{Q}$, standard deviations of the logarithmic distribution of perfusion; log SD$\dot{V}$, standard deviations of the logarithmic distribution of ventilation; $\dot{Q}$ mean, mean $\dot{V}_A/\dot{Q}$ of the perfusion distribution; $\dot{V}$ mean, mean $\dot{V}_A/\dot{Q}$ of ventilation distribution.

difference between the uppermost and lowermost 5-cm segments being threefold for ventilation and tenfold for perfusion. This change results in a mean $\dot{V}_A/\dot{Q}$ ratio of approximately 1 somewhere in the middle of the lung and a range of $\dot{V}_A/\dot{Q}$ ratios (0.5 at the bottom, 5.0 in the apex; see Fig. 19-23, upper panel, the perfusion distribution being a simplified drawing of Fig. 19-11).

Another way of showing the matching between ventilation and blood flow is by illustrating a multicompartmental analysis of ventilation and distribution of blood flow against $\dot{V}_A/\dot{Q}$ ratios. This can be achieved with MIGET.[156] In short, MIGET is based on the constant intravenous infusion of a number of inert gases (usually six) with differing solubilities in blood. When passing through the lung capillaries, the different gases are eliminated via the alveoli and expired in indirect proportion to their solubility. A poorly soluble gas will rapidly leave the bloodstream and be more or less completely eliminated and exhaled (e.g., sulfur hexafluoride); a gas with a high solubility in blood will be almost completely retained in the blood and will not be exhaled (e.g., acetone); and a gas of intermediate solubility will be retained (and expired) to an intermediate extent (e.g., halothane).

As a result, the concentration of the different gases in arterial blood will differ, with higher concentrations of gases with high solubility. Retention can be calculated as the ratio between arterial and mixed venous blood concentrations. Similarly, the ratio of the concentrations (i.e., expired:mixed venous) can be calculated and gives the excretion for each gas. With knowledge of the retention, excretion, and solubility of each gas, an essentially continuous distribution of blood flow against $\dot{V}_A/\dot{Q}$ ratios can be constructed. The lower panel in Figure 19-23 shows an example from a healthy subject. Note that ventilation and blood flow are well matched, being distributed to a limited number of compartments centered on a $\dot{V}_A/\dot{Q}$ ratio of 1. MIGET has a high discriminatory capacity of detecting different $\dot{V}_A/\dot{Q}$ disturbances, but does not provide topographic information. Several variables that reflect the degree of mismatch can be calculated and are shown in Table 19-3. In the following paragraphs, examples of $\dot{V}_A/\dot{Q}$ mismatch are discussed.

If ventilation and perfusion are not matched, gas exchange will be affected. The most common cause of impaired oxygenation is $\dot{V}_A/\dot{Q}$ mismatch. Low $\dot{V}_A/\dot{Q}$ will impede oxygenation because ventilation is insufficient to fully oxygenate the blood, and the degree of impairment is dependent on the degree of $\dot{V}_A/\dot{Q}$ mismatch; in fact, even normal lung regions $\dot{V}_A/\dot{Q}$ (0.5 to 1) cannot completely saturate the blood. Thus, PaO_2 cannot equal alveolar PO_2, and a difference ($PAO_2 - PaO_2$) of 3 to 5 mm Hg (0.4 to 0.7 kPa) is normal. With more $\dot{V}_A/\dot{Q}$ mismatch, the PAO_2–PaO_2 difference is further increased. The $\dot{V}_A/\dot{Q}$ mismatch can account for all the hypoxemia seen in a patient with severe obstruction.[116] Shunt ($\dot{Q}$, but no $\dot{V}_A$), which is often claimed to exist in patients with COPD, is mostly absent when analyzed with a more sophisticated technique such as MIGET. Indeed, shunt in a patient with obstruction likely represents a complicating factor in the disease (Fig. 19-26).

In severe asthma, a distinct bimodal pattern of low ratios occurs when using MIGET[157] (see Fig. 19-26). The reason may be that alveoli behind airways obstructed by edema (or a mucous plug or spasm) can still be ventilated by collateral ventilation (i.e., alveolar pores, interbronchial communications); these regions would otherwise be shunt (no $\dot{V}_A$, some $\dot{Q}$), resulting in the additional peak in $\dot{V}_A/\dot{Q}$ explaining the bimodal distribution. Such collateral ventilation might be part of the reason that true shunt is not normally seen in COPD. Of course, if the standard shunt equation is used to explain hypoxemia, there is no capacity to distinguish between the contributions of low $\dot{V}_A/\dot{Q}$ vs. shunt to hypoxemia (the net effect is best called *venous admixture*).

Airway obstruction is distributed unevenly, and a large variation in $\dot{V}_A/\dot{Q}$ ratios results. Indeed, ventilation is redistributed from regions with high airway resistance to other regions that can then become overventilated in proportion to their perfusion; this causes high $\dot{V}_A/\dot{Q}$ ratios. There are normally regions in the apex that have $\dot{V}_A/\dot{Q}$ ratios of up to 5, but ratios of 100 or more exist in patients with obstruction, making the regions practically indistinguishable from true dead space; this is what causes the increase in physiologic dead space in obstructive lung disease. The effect of high $\dot{V}_A/\dot{Q}$ is also the same as for airway dead space—that is, ventilation that seems not to participate in gas exchange ("wasted ventilation"). Consequently, a patient with COPD has low $\dot{V}_A/\dot{Q}$ (impedes oxygenation) and high $\dot{V}_A/\dot{Q}$ (mimics dead space, impedes CO_2 elimination). However, MIGET is a complex, research-orientated tool, and the calculation of dead space for clinical purposes relies instead on expired CO_2. Derivation of the CO_2 dead space is shown in Box 19-3.

$\dot{V}_A/\dot{Q}$ mismatch exists to varying degrees in all patients with COPD, and it fully explains hypoxemia in most of them. Hypoventilation can also contribute, whereas impaired diffusion or shunt rarely contributes to hypoxemia. Diffusion capacity, or transfer test, can be reduced markedly in severe COPD, in particular in emphysema; in this case the decrease is not caused by thickened alveolar-capillary membranes but rather by reduced capillary blood volume and reduced area for diffusion.

Pulmonary vessels can be affected by lung disease and can cause $\dot{V}_A/\dot{Q}$ mismatch by impeding regional blood flow. Systemic diseases with vascular involvement can cause severe pulmonary dysfunction because of $\dot{V}_A/\dot{Q}$

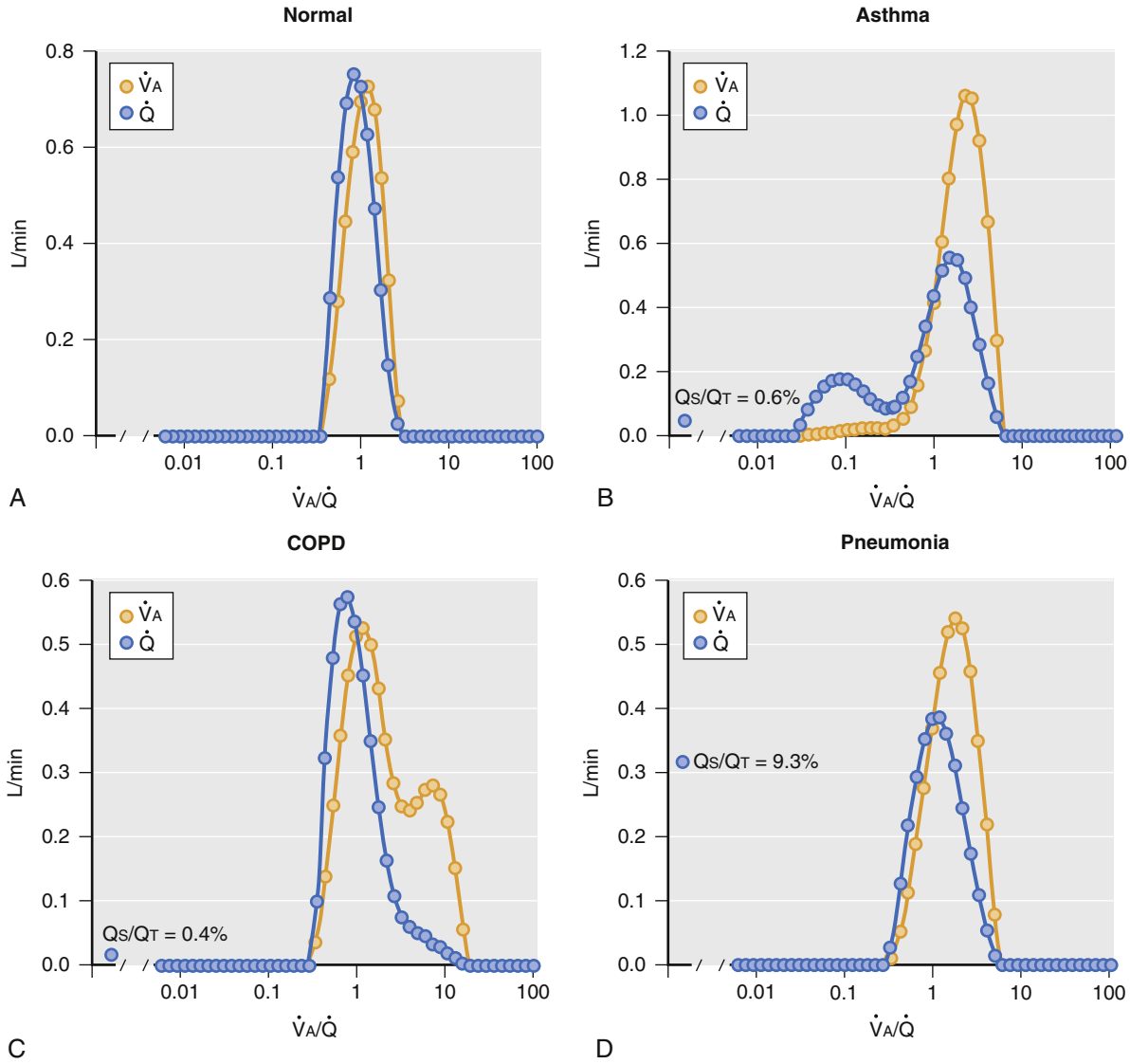


Figure 19-26. Distribution of ventilation and perfusion in normal lungs, asthma, chronic obstructive pulmonary disease (COPD), and pneumonia. **A,** In normal lungs **(A)** there is good matching between ventilation (o) and perfusion (•) with a mode centerd around a $\dot{V}_A/\dot{Q}$ ratio of 1. This results in near optimal oxygenation of blood and CO_2 removal. **B,** In asthma **(B)** there is broader distribution of $\dot{V}_A/\dot{Q}$ with some regions being ventilated well in excess of perfusion ($\dot{V}_A/\dot{Q}$ = 10 and greater), with another mode of low $\dot{V}_A/\dot{Q}$ centred around a ratio of 0.1. This mode can be explained by collateral ventilation maintaining gas exchange in alveoli behind occluded airways. There is no shunt seen in asthma. **C,** In COPD **(C)** the pattern is similar to asthma, but with an additional "high" $\dot{V}_A/\dot{Q}$ mode that adds to dead space such as ventilation. Shunt is not present, and the pattern of $\dot{V}_A/\dot{Q}$ distribution is not associated with significant hypoxemia. **D,** In lobar pneumonia **(D)** the major finding is pure shunt (consolidated, perfused, and poorly ventilated lobe); there is only minor widening of the $\dot{V}_A/\dot{Q}$ distribution.

mismatch, impaired diffusion, and shunt. $\dot{V}_A/\dot{Q}$ mismatch causes most of the hypoxemia in pulmonary fibrosis.[158] In addition, hypoxemia can be caused by impaired diffusion (in particular, during exercise, when it can dominate) and a varying degree of shunt (discussed later).

Pulmonary emboli cause $\dot{V}_A/\dot{Q}$ mismatch in three ways. First, vascular beds are occluded, causing extremely high $\dot{V}_A/\dot{Q}$ locally; this is manifest as increased dead space. Second, the occluded vascular bed diverts blood flow to other, already ventilated regions, thus converting these into low $\dot{V}_A/\dot{Q}$ regions. Finally, if P_{PA} (pulmonary artery pressure) is markedly increased, then any propensity to shunt will be increased.[159] In patients with acute pulmonary embolism,[160] hypoxemia appears to be principally caused by increased variability of $\dot{V}_A/\dot{Q}$, and this has been confirmed experimentally.[161]

Pneumonia involving large areas of consolidated, edematous, or atelectatic (i.e., all non-aerated) lung involves significant shunt, and areas of partial aeration contribute to $\dot{V}_A/\dot{Q}$ mismatch (see Fig. 19-26).[150] In bacterial pneumonia, HPV appears to be inhibited, which is an important mechanism that worsens hypoxemia.[162,163]

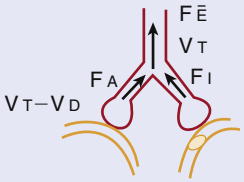
EFFECT OF $\dot{V}_A/\dot{Q}$ ON CO_2 ELIMINATION

A common perception is that although $\dot{V}_A/\dot{Q}$ impedes oxygenation, it has little effect on CO_2 clearance. Actually, elimination of CO_2 is even more limited by $\dot{V}_A/\dot{Q}$ mismatch than is oxygenation of blood[84]; however this seldom results in hypercapnia because minimal increases in $\dot{V}_A$ rapidly correct Pa_{CO_2}. If alveolar ventilation is

BOX 19-3 ***Derivation of the Physiologic Dead Space Equation***

The quantity of CO_2 expired in an exhaled tidal volume = $F_ECO_2 \times V_T$

This comes from perfused lung and from nonperfused lung.



CO_2 exhaled from perfused lung = $F_ACO_2 \times V_A = F_ACO_2 \times (V_T - V_D)$

CO_2 from nonperfused (dead space) lung is derived from inspired gas = $F_ICO_2 \times V_D$

Thus, $F_ECO_2 \times V_T = F_ACO_2(V_T V_D) + (F_ICO_2 \times V_D)$

By rearranging,

$$\frac{V_{DS}}{V_T} = \frac{F_A - F_E}{F_A - F_I}$$

If $F_I = 0$, F is replaced by P, and P_A is replaced by Pa, for CO_2,

$$\frac{V_{DS}}{V_T} = \frac{Paco_2 - P_Eco_2}{Paco_2}$$

where F_E, F_A, and F_I are mixed expired, alveolar, and inspired gas concentration, respectively, and V_T, V_{DS}, and V_A are tidal volume, dead space, and part of the tidal volume to perfused alveoli, respectively.

already impaired and cannot be increased, the addition of $\dot{V}_A/\dot{Q}$ mismatch will increase $Paco_2$.

IMPAIRED DIFFUSION

Hypoxemia can occur because of impaired diffusion in fibrosis or vascular diseases because of severely thickened of the alveolar-capillary membranes. Diffusion is slowed down and the entire length of capillary may be required before the capillary blood has been fully oxygenated, even in resting conditions. On the other hand, this means that a diffusion barrier is unlikely to cause hypoxemia provided the perfusion time and distance permits O_2 equilibration (see Fig. 19-12); however, when these reserves are spent, PaO_2 begins to fall. This decrease is particularly noticeable in patients with pulmonary fibrosis, who might have normal PaO_2 at rest but show dramatic decreases during exercise.[84,116] Development of, or increase in right-to-left shunting in the heart, such as atrial septal defect, can also cause this exercise-induced hypoxemia because the left-to-right shunt at rest becomes right-to-left (or a small right-to-left shunt increases) because of increased P_{PA}.

RIGHT-TO-LEFT SHUNT

If blood passes through the lung without contacting ventilated alveoli, then the blood will not oxygenate or release CO_2. This condition is called a *shunt*, and it lowers PaO_2 and can increase $Paco_2$. Healthy people have a small shunt (2% to 3% of cardiac output) that is caused by venous drainage of the heart muscle into the left atrium by the Thebesian veins. In pathologic states, the shunt ranges from 2% to 50% of cardiac output.

Shunt is often confused with $\dot{V}_A/\dot{Q}$ mismatch. While a $\dot{V}_A/\dot{Q}$ of zero (some perfusion, no ventilation) constitutes a shunt, there are two clear and important differences between low $\dot{V}_A/\dot{Q}$ and shunt. First, the anatomy of a shunt differs from an area of low $\dot{V}_A/\dot{Q}$. Regions with low $\dot{V}_A/\dot{Q}$ are characterized by narrowing of the airways and vasculature, which reduces ventilation and blood flow in some regions and increases them in others. Examples are obstructive lung disease and vascular disorders. Shunt is caused by the complete cessation of ventilation in a region, usually as a result of collapse (atelectasis) or consolidation (e.g., pneumonia). Asthma or COPD does not involve the formation of a shunt[116]; if a shunt is present, it indicates a complication. Second, supplemental O_2 improves the hypoxemia caused by low $\dot{V}_A/\dot{Q}$, but it has less effect on hypoxemia caused by shunt. Although aeration may be poor in regions of low $\dot{V}_A/\dot{Q}$, aeration does exist in these regions, and the concentration of O_2 in these alveoli can be enriched by increasing Fio_2. In contrast, supplemental O_2 cannot access the alveoli in a true (anatomic) shunt.

Anatomic shunt and low $\dot{V}_A/\dot{Q}$ usually coexist, and the net effect is sometimes referred to as *percent shunt* (per the standard shunt equation). In this situation, the low $\dot{V}_A/\dot{Q}$ component will contribute to the response from increasing Fio_2, and the regions of anatomic (true) shunt will not; therefore, shunt will always lower PaO_2 (at any Fio_2). When the calculated fraction increases to 25%, the response to increased Fio_2 will be small; when it increases to 30% or greater, the response will be negligible.[150] This varying response is the net effect of mixing blood with normal pulmonary end-capillary PO_2 and shunt blood, which has the same PO_2 as mixed venous blood. If shunt is a large enough fraction of total lung blood flow, the additional O_2 that can be physically dissolved by the raised Fio_2 is so small that it is almost immeasurable; such a shunt is said to be refractory.

RESPIRATORY FUNCTION DURING ONE-LUNG VENTILATION

Oxygenation can be a challenge during one-lung surgery. One lung is not ventilated but is still perfused, and in the postoperative period, restoration of lung integrity and ventilation–perfusion matching can take time (see Chapter 66).[164]

The technique of one-lung anesthesia and ventilation means that only one lung is ventilated and that the lung provides oxygenation of—and elimination of carbon dioxide from—the blood. Persisting perfusion through the nonventilated lung causes a shunt and decreases PaO_2 (Fig. 19-27); measures can be taken to reduce this blood flow.[165,166]

During one-lung anesthesia, there are two main contributors to impaired oxygenation: (1) the persisting blood flow through nonventilated lung and (2) development of atelectasis in the dependent lung, resulting in local shunt and low $\dot{V}_A/\dot{Q}$.[139] A recruitment maneuver can dissect the influence of the dependent atelectasis[167]; serial increases in peak airway pressure and PEEP directed to the dependent, ventilated lung increased significantly the PaO_2, indicating that dependent atelectasis was an important cause of hypoxemia. In this situation, diversion of perfusion from the dependent (ventilated) to the

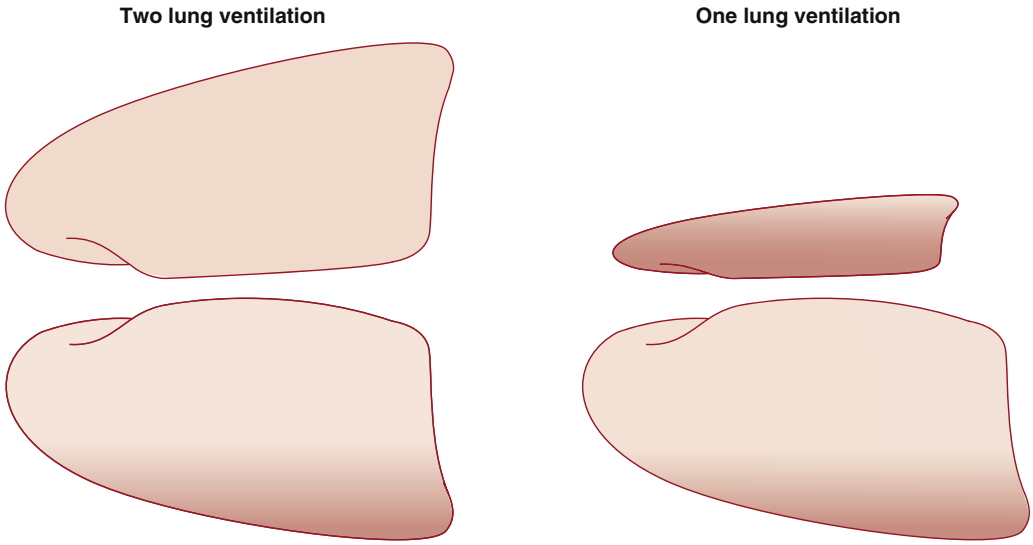


Figure 19-27. Schematic drawing of the distribution of shunt during two-lung ventilation and one-lung ventilation during anesthesia. Shunt region is indicated by dark area in the lower lung during two-lung ventilation and in the lower lung—plus the entire upper lung—during one-lung ventilation.

nondependent (i.e., nonventilated) lung would have worsened oxygenation and not improved it.

Recruitment can also affect V_D. Recruitment during one-lung anesthesia improved oxygenation, but also decreased V_D.[168] The slope of the CO_2 curve during a tidal expiration (phase III) was flatter, indicating a more even distribution of inspired gas throughout the lung and more synchronous alveolar emptying. Thus, a secondary effect of recruiting collapsed lung tissue can be (presumably not when recruitment causes overinflation) more even distribution of ventilation and a decrease in the dead space fraction. This effect should facilitate the use of a smaller V_T. In contrast to an individual recruitment, the application of continuous elevated P_{AW} (PEEP titrated to optimal compliance in the ventilated lung) increased compliance by 10% but slightly worsened oxygenation, probably because of redistribution of blood from the ventilated to the nonventilated (nondependent) lung.[169] The rationale for identifying and using optimal PEEP has also been reviewed.[170]

Maneuvers can also be applied to the nondependent lung. The effects of compressing the nondependent lung on oxygenation were examined using an intra-arterial O_2 sensor, which provides instantaneous and continuous PaO_2.[171] Compression resulted in increased PaO_2, suggesting a shift of blood flow from the nondependent (nonventilated) to the dependent (ventilated) lung; development of complete absorption atelectasis in the nondependent lung may have similar effects.[172]

Inhaled nitric oxide (NO; pulmonary vasodilator) and intravenous almitrine (pulmonary vasoconstrictor) have been studied alone and in combination (see Chapter 104). NO alone has little effect,[173] but oxygenation is improved when NO is combined with almitrine.[174,175] Almitrine alone also improves oxygenation[176] at a dose that does not alter P_{PA} or cardiac output. Although inhaled NO increases perfusion to already ventilated regions (increasing $\dot{V}_A/\dot{Q}$), almitrine potentiates HPV, decreasing perfusion to nonventilated (i.e., shunt) areas (reducing shunt) and potentially diverting blood flow to ventilated regions of the lung. Selective pulmonary vasodilation is reviewed.[177,178]

Careful analysis of the mechanical obstruction caused by kinking of pulmonary vessels and by HPV has shown that HPV is the important determinant of diversion of blood flow away from nonventilated lung (though not complete).[179] Moreover, positioning of the patient can affect the degree of shunting.[180]

PNEUMOPERITONEUM

Laparoscopic operations are usually performed by insufflation of CO_2 into the abdominal cavity The effects are twofold. First, the consequences of hypercapnic acidosis[181,182] include depressed cardiac contractility, sensitization of the myocardium to the arrhythmogenic effects of catecholamines, and systemic vasodilation.[183] There can also be long-lasting postoperative effects on breathing control.[184] In addition, the physical effects of pneumoperitoneum are important. These include decreased FRC and VC,[185] formation of atelectasis,[186] reduced respiratory compliance,[187] and increased peak airway pressure.[188] Nonetheless, shunt is reduced and arterial oxygenation is mostly improved during CO_2 pneumoperitoneum.[189] This paradox—more atelectasis and less shunt—suggests that efficient redistribution of blood flow away from collapsed lung regions is attributable to hypercapnic acidosis CO_2. Indeed, a recent experimental study showed that if the abdomen was inflated with air, a much larger shunt developed than if CO_2 had been used for inflation.[190]

LUNG FUNCTION AFTER CARDIAC SURGERY

Cardiac surgery produces the greatest degree of atelectasis in the postoperative period (see Chapter 67),[191] perhaps because both lungs are often collapsed. Spontaneous resolution of the atelectasis is gradual, leaving a residual shunt of up to 30% by day 1 or 2[99,192]; however, recruitment at the end of the case is possible. In some cases, 30 cm H_2O for 20 seconds is sufficient,[99] facilitated by the chest being open. A recruitment maneuver

(with zero PEEP) causes transient increase in PaO_2 and EELV, and with PEEP alone EELV was increased but PaO_2 unchanged; however, a recruitment maneuver followed by PEEP resulted in a large and sustained increase in both Pa_{O_2} and EELV.[193] The separation of effect whereby PEEP alone increases EELV to a greater extent than it increases oxygenation suggests further opening of already opened lung rather than opening of atelectatic lung.

Head-to-head comparison of intermittent CPAP versus constant noninvasive pressure support ventilation reported intriguing findings. There was less radiographic evidence of atelectasis following pressure support, without differences in oxygenation of bedside pulmonary function testing.[194] Although the authors' conclusion was no clinical benefit with noninvasive pressure support ventilation, differences in Fio_2 could cause differences in propensity to atelectasis. Recruitment maneuvers up to moderately high levels of airway pressure (46 cm H_2O) do not appear to affect the pulmonary vascular resistance or right ventricular afterload,[195] which is an issue of considerable importance following cardiac surgery. Nonetheless, it is prudent to consider RV loading and ejection in such circumstances, especially in the setting of diminished RV reserve or tricuspid regurgitation. Finally, many cardiac surgeries are now being performed "off pump," and the postoperative pulmonary effect is reduced, with less postoperative intrapulmonary shunt and correspondingly shorter hospital stays.[196]

POSTOPERATIVE PHYSIOTHERAPY

Physiotherapy, much debated after surgery (including cardiac surgery; see Chapter 103)[197] is associated with more effective lung recruitment (seen on thoracic CT) when involving deliberate approaches, such as flow bottles following exercise.[198] In effect, large and early inspiration following surgery may be key to preventing postoperative lung complications. Whether the deep inspiration needs to be accomplished with a specific forced breathing device is uncertain.

EFFECT OF SLEEP ON RESPIRATION

Sleep has a major effect on many aspects of respiration, perhaps the most obvious being ventilation.[199] Sleep reduces V_T and inspiratory drive, and $\dot{V}_E$ falls by approximately 10%, depending on the sleep stage, with the most marked fall occurring during rapid-eye-movement (REM) sleep. Lung volume (i.e., FRC) is also reduced[200]; this commences almost immediately after the onset of sleep, and the lowest levels of FRC (down to 10% of resting levels) occur in REM sleep.[201] CT studies in healthy volunteers demonstrate that the sleep-induced decrease in FRD is accompanied by reduced aeration in the dependent lung. Such loss in aeration was demonstrated in anesthetized patients when their Fio_2 was increased from 0.3 to 1.0; atelectasis developed rapidly. It is possible that during normal sleep, breathing with high levels of O_2 would also cause atelectasis.

Complete references available online at expertconsult.com

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