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1 Respiratory Physiology in Critical Illness

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Goals

- Describe the basic lung volumes and capacities and the fundamentals of breathing mechanics.
- Describe airway resistance, lung compliance, and thoracic wall compliance as major components of pulmonary ventilation.
- Distinguish restrictive physiology from obstructive physiology.
- Describe common patterns of increased work of breathing and their associated factors.
- Describe the mechanisms of hypoxemia.

Introduction

The fundamental pillars of critical care medicine are the management of the lungs, heart, and kidneys and the provision of nutritional support. The practice of critical care medicine is often defined by abnormal respiratory physiology and requires detailed knowledge of lung mechanics, the mechanism of hypoxia, and the control of breathing. Therefore, laboratory assessment in pulmonary disorders is useful (Table 1.1; Box 1.1). Before the lungs can enable gas exchange, air must move from the upper airway down a series of branching small airways and reach the alveoli. In the walls of the alveoli, capillaries form a dense network and receive blood flowing from the pulmonary artery (from the right ventricle) before it flows to the pulmonary vein (and then to the left atrium). Between the capillary network and the alveoli lies a thin blood-gas barrier through which oxygen (O_2) and carbon dioxide (CO_2) move, chiefly by simple diffusion.

At rest, inspiration and expiration generate *tidal volume*. After the tidal volume is exhaled, further forceful expiration generates *expiratory reserve volume*. The volume of air remaining in the lung is the *residual volume*. After resting inspiration, forceful inspiration to maximal capacity generates *inspiratory reserve volume*. Volume that can be generated by maximal inspiration to maximal expiration is called *vital capacity* (Figure 1.1). Normal vital capacity is around 3 to 5 L, and normal tidal volume is approximately 500 mL. *Total minute ventilation* is the product of the tidal volume times the respiratory rate per minute.

Mechanics of Breathing

During rest, inspiration is active and expiration is passive. The most important muscle of inspiration is the diaphragm. When it contracts, the abdominal contents are forced downward and forward, and the vertical dimension of the chest cavity is increased. The external thoracic muscles make the rib margins lift and move out, increasing the transverse diameter of the thorax during forceful inspiration. At functional residual capacity, the rib cage acts as an outward force that generates negative pleural pressure. At end-expiration, the diaphragm prevents the abdominal organs from encroaching on the thoracic space and influencing the lung in the supine or prone position. During spontaneous breathing, these muscles expand the lung, creating even more negative intrapleural pressure and resulting in inspiration. During mechanical ventilation, positive pressure from the ventilator expands the chest wall, but the intrapleural pressure is positive.

Airway Resistance and Lung Compliance

Pulmonary ventilation and the work of breathing depend on the airway resistance and compliance of the lungs and the thoracic cage. *Airway resistance* is the pressure difference between the alveoli and the mouth divided by the flow rate. Most airway resistance is produced in medium-sized bronchi rather than in small bronchioles. The bronchial smooth muscles, located in medium-sized bronchi, are innervated by the autonomic nervous system. Stimulation of β-adrenergic receptors causes bronchodilation;

Table 1.1 • Useful Laboratory Values in Pulmonary Disorders

Laboratory Value	Significance in Pulmonary Disorders
Arterial blood gas	Hypoxia, hypercapnia, acidosis, alkalosis
Hemoglobin, glucose, urea nitrogen, creatinine, electrolytes, calcium, phosphorus, thyrotropin	Nonpulmonary causes of dyspnea
Plasma brain natriuretic peptide	Pulmonary edema due to heart failure
Serum bicarbonate	Chronic hypercapnia in COPD or obesity-hypoventilation syndrome
$Alpha_1$-antitrypsin	$Alpha_1$-antitrypsin deficiency, obstructive pattern
Eosinophils	Allergic asthma, parasitic infection, drug reaction, syndromes of pulmonary infiltrates with eosinophilia
Procalcitonin	Bacterial pneumonia
C-reactive protein	Pneumonia
Rheumatologic serology (ANA, RF, antisynthetase antibodies, CK, aldolase, SS-A/SS-B, Scl-70)	Interstitial lung disease
Anti-GBM antibody, ANCA	Pulmonary hemorrhage
Polycythemia	Recurrent hypoventilation or obstructive sleep apnea–associated hypoxemia

Abbreviations: ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic autoantibody; CK, creatine kinase; COPD, chronic obstructive pulmonary disease; GBM, glomerular basement membrane; RF, rheumatoid factor.

parasympathetic activity causes bronchoconstriction and increased airway resistance. Lung volume has an important effect on airway resistance: As lung volume decreases, airway resistance increases. Small airways may even close completely at low lung volumes.

Lung compliance is defined by the volume change per unit pressure change. Furthermore, it has 2 components: static and dynamic lung compliance.

Static Lung Compliance

Lung tends to collapse at any degree of pulmonary inflation, whereas the chest wall tends to recoil outward. This natural trend represents compliance of both the lung and the chest wall in static pressure-volume curves (Figure 1.2).

Lung compliance changes with various nonparenchymal conditions. Patients with obesity, ascites, or intra-abdominal hypertension have a stiffer chest wall; the lung and total respiratory system compliance curves shift down and rightward. In contrast, massive aspiration, alveolar edema, or fibrotic lung disease decreases the lung and total respiratory system compliance. In a patient with acute respiratory distress syndrome (ARDS), lung volume is further reduced and compliance is decreased. In addition, the overall volume of tissue and chest wall may be affected by illness, so that in ARDS the net effect on pleural pressure is unpredictable.

Static airway pressure of the respiratory system correlates with plateau pressure during mechanical ventilation. Moreover, the plateau pressure also represents the intra-alveolar pressure during use of an end-inspiratory hold. In passive ventilation, such as when patients are deeply sedated or paralyzed, the chest wall compliance curve tracks the pleural pressure. Thus, pressure measured with an esophageal balloon can be used to approximate these measures.

Dynamic Lung Compliance

Dynamic pressure-volume curves during inspiration and expiration exhibit a different pattern. This phenomenon, *hysteresis*, can be explained by surface tension variation at the alveolar air-fluid interface during inspiration and expiration. Pulmonary surfactant, a natural substance produced by type II epithelial cells in the lung, reduces the surface tension of the fluid layer lining the alveoli. During inspiration, alveolar surface tension increases because pulmonary surfactant spreads over a wider alveolar surface. The reverse occurs during expiration, when pulmonary surfactant condenses over a smaller alveolar surface.

Work of Breathing

Work is required to move the lung and the chest wall. The area under the dynamic pressure-volume curve of the lungs is used to estimate the work of breathing (WOB). During inspiration, the *elastic* WOB is the work needed to overcome elastic forces of the chest wall, lung parenchyma, and alveolar surface tension. In addition, *resistive* WOB is needed during inspiration to overcome tissue and airway resistance. During expiration, only resistive WOB is needed. Hence, increased WOB occurs with higher breathing rates

Box 1.1 • Interpretation of Blood Gas Data

Step 1. Determine whether the primary condition is *acidemia* (pH <7.35) or *alkalemia* (pH >7.45).

Step 2. Determine whether the disorder is *metabolic* (pH and $Paco_2$ changes are in the same direction) or *respiratory* (pH and $Paco_2$ changes are in the opposite direction).

Step 3. Determine whether compensation is adequate.

Metabolic acidosis: $Paco_2 = (1.5\ [HCO_3^-]) + 8\ (\text{Correction} \pm 2)$

Acute respiratory acidosis: Increase in $[HCO_3^-] = \Delta Paco_2/10\ (\text{Correction} \pm 3)$

Chronic respiratory acidosis: Increase in $[HCO_3^-] = 3.5\ (\Delta Paco_2/10)$

Metabolic alkalosis: Increase in $Paco_2 = 40 + 0.6\ (\Delta HCO_3^-)$

Acute respiratory alkalosis: Decrease in $[HCO_3^-] = 2\ (\Delta Paco_2/10)$

Chronic respiratory alkalosis: Decrease in $[HCO_3^-] = 5\ (\Delta Paco_2/10)$ to $7\ (\Delta Paco_2/10)$

Step 4. Calculate the anion gap (AG):

$$AG = [Na^+] - [Cl^-] + [HCO_3^-] - 12 \pm 2.$$

If the AG is elevated (>12), calculate the osmolar (OSM) gap (normal is <10):

$$\text{OSM Gap} = \text{Measured OSM} - (2\ [Na^+]) - (\text{Glucose}/18 - \text{SUN}/2.8).$$

Step 5. If an AG is present, calculate the delta-delta ratio:

$$\text{Delta} - \text{Delta Ratio} = \Delta AG / \Delta[HCO_3^-].$$

If <1, a concurrent non-AG metabolic acidosis is likely present. If >2, a concurrent metabolic alkalosis is likely present.

Abbreviations: Cl^-, chloride; Δ, change in; HCO_3^-, bicarbonate; Na^+, sodium; SUN, serum urea nitrogen.

Data from Kaufman DA. Interpretation of arterial blood gases (ABGs) [Internet]. New York: American Thoracic Society. c2017 [cited 2017 Sep 5]. Available from: http://www.thoracic.org/professionals/clinical-resources/critical-care/clinical-education/abgs.php.

and faster flow rates. With a larger tidal volume, the elastic WOB is larger. Patients with stiff lungs tend to take small rapid breaths, and patients with severe airway obstruction breathe more slowly.

Closing Capacity

Lung cannot be completely empty because of airflow-limiting segments in the small airways. Hence, expiration after development of airflow-limiting segments is effort independent. What remains in the lungs when small airways start to close is called the *closing capacity*. Patients with airway disease (eg, asthma, chronic obstructive pulmonary disease [COPD], or cystic fibrosis) are predisposed to having a higher closing capacity, leaving a large residual volume. The volume of air expired between closing capacity and residual volume is called the *closing volume*.

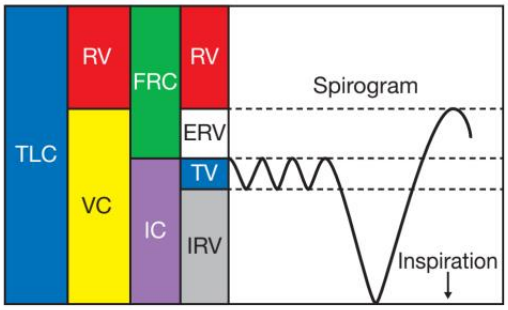

Figure 1.1. *Standard Lung Volumes and Capacities. After resting inspiration, forceful inspiration to maximal capacity generates inspiratory reserve volume. The volume that can be generated by maximal inspiration to maximal expiration is the vital capacity (VC). ERV indicates expiratory reserve volume; FRC, functional residual capacity; IC, inspiratory capacity; IRV, inspiratory reserve volume; RV, residual volume; TLC, total lung capacity; TV, tidal volume.*

Changes in Lung Mechanics in Acute Respiratory Failure

In patients who are critically ill with respiratory failure, 2 types of physiologic derangement occur: obstructive and restrictive.

Obstructive Physiology

In obstructive lung diseases, pulmonary compliance is normal or increased, but airway resistance is increased, especially during expiration. As mentioned above, normal expiration is passive. However, with obstructive physiology, such as in patients with asthma or COPD, extra work is needed for adequate expiration.

Restrictive Physiology

Pneumonia and ARDS are examples of diseases with restrictive physiology in which compliance of the lung, or chest wall (or both) is decreased. The static pressure-volume curve of the lungs or chest wall (or both) is shifted rightward. The transpulmonary pressure (alveolar pressure minus pleural pressure) indicates the pressure across the alveolus and therefore across the pulmonary capillary bed. Decreased compliance of the lungs requires

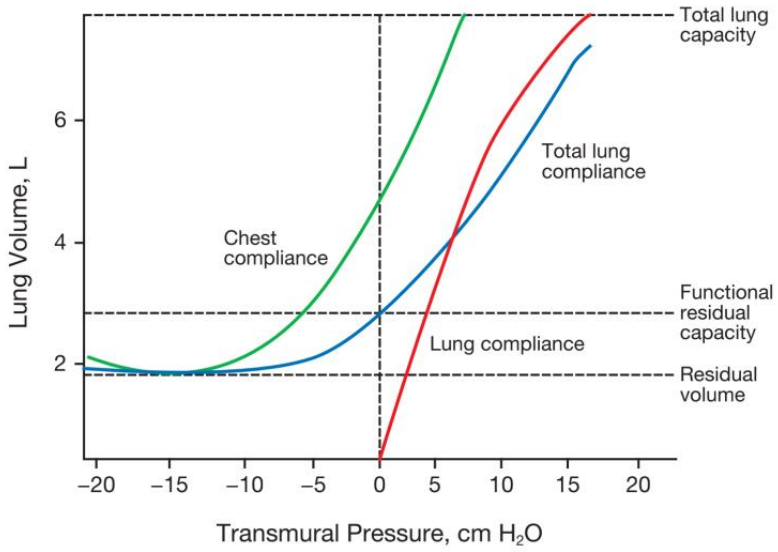

Figure 1.2. *Compliance Curves. Compliance curves for lung and chest are shown along with total lung compliance. At small lung volumes, the negative transmural pressure of chest compliance indicates the chest wall's natural tendency to spring outward and expand. Lung compliance is high (ie, the slope of the curve is steep) at low lung volumes and decreases as the lung expands. Functional residual capacity is the summation of transmural pressures generated by the chest wall and lung when they are equal and opposing.*

increased transpulmonary pressure for tidal inspiration. Further, the elastic WOB required for inspiration is increased and is usually compensated for by rapid shallow breathing. The intrinsic causes of restrictive physiology are interstitial lung diseases, pneumonia, and ARDS, and the extrinsic causes include respiratory muscle weakness, chest deformities, cardiomegaly, hemothorax, pneumothorax, empyema, and pleural effusion or thickening.

Respiratory Mechanics Affecting Circulation

Higher transpulmonary pressure leads to greater impedance to right ventricular outflow through the pulmonary vascular tree. A high right ventricular afterload decreases right ventricular output. Right ventricular preload depends on the degree of intrapleural pressure. With mechanical ventilation, intrapleural pressure increases during inspiration, further decreasing right ventricular preload. A stiffened chest wall increases intrapleural pressure, decreasing right ventricular preload further. Use of positive end-expiratory pressure and the prone position can also decrease right ventricular preload by increasing intrapleural pressure and stiffening the chest wall, respectively.

Neurogenic Pulmonary Edema

Acute central nervous system events such as acute head injury, seizure, tumors, and intracranial or subarachnoid hemorrhages can induce acute pulmonary edema within minutes or as late as 12 to 24 hours after the event. Besides having acute shortness of breath from pulmonary edema, patients may have fever, tachycardia, hypertension, and leukocytosis from sympathetic surge. The proposed pathophysiology is that the neuronal damage increases sympathetic tone with a catecholamine surge, which subsequently increases systemic vascular resistance and decreases left ventricular contractility, causing alveolar capillary leakage and eventually leading to a severe increase in intracranial pressure. Management is primarily supportive. α-Blockers can be used, and excessive diuresis should be avoided. The key is to treat the underlying central nervous system insult and the increased intracranial pressure.

Physiology of Hypoxia

Changes in Diffusing Capacity in Critical Illness

Gases move across the blood-gas barrier by diffusion. The O_2 diffusion reserve of the normal lung is enormous. However, in patients with alveolar hypoxia and thickening of the blood-gas barrier, O_2 diffusion is challenged.

Pulmonary Vascular Resistance

Pulmonary vascular resistance is usually small and can further decrease by recruitment and distention of capillaries. Pulmonary vascular resistance increases at high and low lung volumes. Hypoxia, serotonin, histamine, thromboxane A_2, and endothelin constrict pulmonary vasculature. Hypoxia constricts small pulmonary arteries probably by the direct effect of the low P_{O_2} on vascular smooth muscle. This mechanism, called *hypoxic pulmonary vasoconstriction*, directs blood flow away from poorly ventilated areas of the diseased lung in the adult.

Nitric oxide, phophodiesterase inhibitors, calcium channel blockers, and prostacyclin dilate pulmonary vasculature. Inhaled pulmonary vasodilators such as nitric oxide or inhaled phophodiesterase inhibitors reduce vascular tone locally in the well-ventilated regions, causing a shift in blood flow away from unventilated regions toward better-ventilated regions. Inhaled nitric oxide has been shown to reduce shunting and improve arterial oxygenation in patients with ARDS. Use of intravenous pulmonary vasodilators, such as prostacyclin, does not change P_{aO_2} much in patients with ARDS and pulmonary hypertension, probably because of the mixed effects of reduced pulmonary arterial pressure, increased cardiac output, and worsened intrapulmonary shunt.

In contrast, systemic vasodilators can produce hypoxemia. Systemic vasodilators increase cardiac output, impair hypoxic vasoconstriction in both well-ventilated and poorly ventilated pulmonary vasculature, and change intracardiac pressure or pulmonary arterial pressure, thereby altering the distribution of pulmonary blood flow. Nitroprusside, hydralazine, nitroglycerine, nifedipine, dopamine, and dobutamine can produce this effect.

Physiology of Hypoxemia

The 5 mechanisms of hypoxemia are hypoventilation, diffusion limitation, shunt, ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch, and low inspiratory O_2 pressure.

Hypoventilation

Hypoventilation always increases the alveolar P_{CO_2}, which leads to lower alveolar P_{aO_2} unless additional O_2 is inspired. The treatment is to provide additional O_2.

Diffusion Limitation

Diffusion of gases is limited when the blood-gas barrier is thickened.

Shunt

This refers to blood that enters the arterial system without going through ventilated areas of the lung. Hypoxemia resulting from a shunt does not improve after adding O_2. If the shunt is caused by mixed venous blood, its size can be calculated from the shunt equation. Shunt is an important cause of hypoxemia in patients with ARDS and pneumonia.

$\dot{V}/\dot{Q}$ Mismatch

$\dot{V}/\dot{Q}$ mismatch is the most common cause of hypoxemia, especially in the perioperative period after general anesthesia. A patient with $\dot{V}/\dot{Q}$ mismatch has a problem with either ventilation (air going in and out of the lungs) or perfusion (O_2 and CO_2 diffusion at the alveoli and the pulmonary arteries). $\dot{V}/\dot{Q}$ ratios compare the amount of air reaching the alveoli to the amount of blood reaching the alveoli. The $\dot{V}/\dot{Q}$ ratio describes the gas exchange in any single lung unit. Regional differences in the $\dot{V}/\dot{Q}$ ratio in the upright lung cause regional changes in gas exchange. The normal $\dot{V}/\dot{Q}$ ratio is about 1, and decreases or increases in the ratio indicate changes in the alveolar gas and end-capillary blood composition. $\dot{V}/\dot{Q}$ mismatch impairs the uptake or elimination of all gases by the lung. Although CO_2 elimination is impaired by $\dot{V}/\dot{Q}$ mismatch, it can be corrected by increasing the ventilation to the alveoli. In contrast, hypoxemia resulting from $\dot{V}/\dot{Q}$ mismatch cannot be resolved by increased ventilation. The difference in the CO_2 and O_2 responses results from their own dissociation curve characteristics. Clinically, regions with low or high $\dot{V}/\dot{Q}$ ratios cause hypoxemia, impaired CO_2 elimination, and increased WOB in COPD patients.

Low Inspiratory O_2 Pressure

Low inspiratory O_2 pressure causes hypoxemia even with a normal alveolar-arterial difference in the partial pressure of O_2.

Changes in Dead Space in Critical Illness

Dead space is the volume (not a space) that is ventilated but does not participate in perfusion. There are 2 types of dead space: anatomical dead space and physiologic dead space. *Anatomical dead space*, normally about 150 mL, is the volume of the conducting airways. *Physiologic dead space* is the volume of gas that does not eliminate CO_2. Because physiologic dead space includes airway and alveolar dead space, it is increased in many lung diseases. Furthermore, increased $\dot{V}/\dot{Q}$ mismatch and shunt are the most likely contributors to increased dead space in ARDS.

Supplemental O_2 and CO_2 Retention in COPD Patients

High fractional supplemental O_2 may cause CO_2 retention in COPD patients because supplemental O_2 may increase the partial pressure of O_2 in the alveoli (P_{AO_2}) in lung units with a low $\dot{V}/\dot{Q}$ ratio, inhibiting regional hypoxic pulmonary vasoconstriction and increasing blood flow to these units. Consequently, blood is diverted away from better-ventilated regions, converting them to lung units with high $\dot{V}/\dot{Q}$ ratios, which increases wasted ventilation.

Supplemental O_2 may cause CO_2 retention in COPD patients through a second mechanism, the Haldane effect. In this phenomenon, increased Pao_2 decreases the binding of both hydrogen ions and CO_2 to hemoglobin, thereby increasing the amount of physically dissolved CO_2 and Pco_2. The decreased respiratory drive from low $Paco_2$ is a less likely cause.

In clinical practice, COPD patients who receive supplemental O_2 to maintain normal Pao_2 do not retain clinically significant levels of CO_2. The use of noninvasive mechanical ventilation can alleviate Co_2 retention while providing enough O_2 in COPD patients.

Indexes of Oxygenation

Of the several indexes of oxygenation that are used, 2 are discussed here: the alveoli-arterial (A-a) gradient and the ratio of Pao_2 to the fraction of inspired O_2 (FIO_2). Both are O_2 tension–based indexes (calculated from Po_2) as opposed to a concentration-based index, such as the shunt index (calculated from the arterial O_2 content). The A-a gradient and the Pao_2/FIO_2 ratio can be affected by the following factors: a shunt, $\dot{V}/\dot{Q}$ mismatch, congenital heart disease, cardiac output, FIO_2, temperature, low Pco_2, and O_2 extraction.

A-a Gradient

The A-a gradient is the gradient between an alveolus and the arterial blood, expressed in millimeters of mercury. PAO_2 is calculated with the following simplified formula (using the sea level barometric pressure of 760 mm Hg, water vapor pressure at 37°C of 47 mm Hg, and a respiratory quotient of 0.8-0.9):

$$P_{AO_2} = (FIO_2 \times 713) - (PaCO_2 \times 1.25).$$

Subsequently, the A-a gradient is calculated as follows:

$$\text{A-a Gradient} = P_{AO_2} - Pao_2.$$

The normal value of the A-a gradient is 7 mm Hg in young patients and 14 mm Hg in elderly patients at 21% FIO_2. The A-a gradient is increased with a higher FIO_2, $\dot{V}/\dot{Q}$ mismatch, a diffusion defect, an intracardiac shunt, or an increased O_2 extraction ratio. A high $Paco_2$ due to alveolar hypoventilation results in a normal A-a gradient, and this is the most useful situation for using the A-a gradient.

Pao_2/FIO_2 Ratio

At sea level, the Pao_2/FIO_2 ratio is normally more than 500 mm Hg; that is, Pao_2 should exceed FIO_2 by 500 times in normal lung. The Pao_2/FIO_2 ratio is used for risk stratification, such as in the Berlin definition of ARDS (eg, <100 indicates severe ARDS). The Pao_2/FIO_2 ratio, in contrast to the A-a gradient, cannot be used to distinguish hypoxemia due to alveolar hypoventilation from hypoxemia due to other causes. Like the A-a gradient, the Pao_2/FIO_2 ratio is dependent on FIO_2 and is highly dependent on the O_2 extraction ratio.

Summary

- Pulmonary ventilation depends on airway resistance and the compliance of the lungs and the thoracic cage.
- Lung compliance is defined by the volume change per unit pressure change. Massive aspiration, alveolar edema, ARDS, or fibrotic lung disease decreases lung compliance.
- A higher breathing rate is accompanied by faster flow rates and larger viscous WOB. With a larger tidal volume, the elastic work is larger.
- Restrictive physiology can occur in patients with pneumonia or ARDS. In these conditions, the compliance of the lung or chest wall (or both) is decreased.
- With obstructive physiology, airway resistance is increased, especially during expiration.
- If transmural pressure for the lungs is zero, the system is neither inflating nor deflating. For a given ventilator volume, the lateral distance between plateau pressure and the chest wall compliance curve is the transpulmonary pressure.
- The 5 mechanisms of hypoxemia are hypoventilation, diffusion limitation, shunt, $\dot{V}/\dot{Q}$ mismatch, and low inspiratory O_2 pressure.
- Dead space is the volume that is ventilated but does not participate in perfusion.

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