Mechanical Ventilation in Neonates and Children

A Pathophysiology-Based Management Approach

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Preface

With so many books on the subject, a reasonable question may be "why another book"? During our careers as clinicians, investigators and educators, we have observed that the healthcare providers are often intimidated by the ventilators as they focus on the machine rather than the altered pathophysiology that is to be addressed in the least injurious fashion while allowing sufficient time for recovery to occur. The ventilator manufacturers do not make it easier by introducing different terminology for similar interventions adding further confusion. We have also observed that nurses, physicians and respiratory therapists have their own areas of attention. We have attempted to provide a common framework based on growth-dependent pulmonary mechanics and underlying pathophysiologic mechanism necessitating all forms of support of the respiratory system. We hope that this framework is an effective tool to understand the underlying pathophysiologic derangements and the therapeutic rationale behind the supportive measures necessary. We also hope that this book will be useful for readers from different disciplines at varying levels of experience, at the bedside as clinicians, in the classrooms as educators and in the academic settings conducting scholarly activities.

We begin with traditional, age-old principles of pulmonary mechanics and physiology of gas exchange taught by Julius Comroe and simplified by John West. These are important for any student to build his/her understanding the fundamentals of lung dysfunction. The concepts of static and dynamic processes are explained and mechanisms of airflow in health and disease are described. Importance of clinical examination and physical assessment is emphasized followed by description of monitoring techniques. Within this framework, we present both invasive and non-invasive support of respiration. Every attempt is made to not only direct the reader what to do but also the rationale for why a certain approach is superior in some situations but not others. A separate section on special challenges encountered in the neonatal period is presented. Finally, we describe various case-based approaches in managing respiratory failure.

This book is intended for medical students, residents, fellows, attending physicians, nurses and respiratory therapists. We dedicate it to countless parents, who entrusted their most precious possession—the lives of their children, to our care; and to all our patients who taught us so much over the years.

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Contents

Chapter 1
Mechanical Characteristics of the Lung and the Chest Wall

Ashok P. Sarnaik

Mechanical properties of the respiratory system govern the principles of air movement between the alveoli and the atmosphere. For air to move from one end to another, a pressure gradient is required. As long as there is some communication between the alveoli and the atmosphere, gas will flow (volume/time) from a higher pressure to a lower pressure until the pressures at both ends equilibrate resulting in cessation of flow. Pressure equilibration is not instantaneous; it requires time. Insufficient time will prevent pressure equilibration, and therefore the potential change in volume. Resistive properties of the respiratory system oppose generation of flow whereas the elastance characteristics oppose change in volume.

1.1 Lung Volumes and Capacities

Along with pressure, knowledge of lung volumes and capacities is crucial to understanding normal lung function as well as many pathological conditions (Fig. 1.1). *Tidal volume* (VT) is the volume of gas moved with each breath. In health, spontaneous VT is usually between 6-8 ml/kg. This volume refreshes alveolar gas with atmospheric air during inspiration and leads to removal of CO_2 during exhalation. The volume of gas remaining in the lung after tidal exhalation is termed *functional residual capacity* (FRC). FRC is measured either by measurement of

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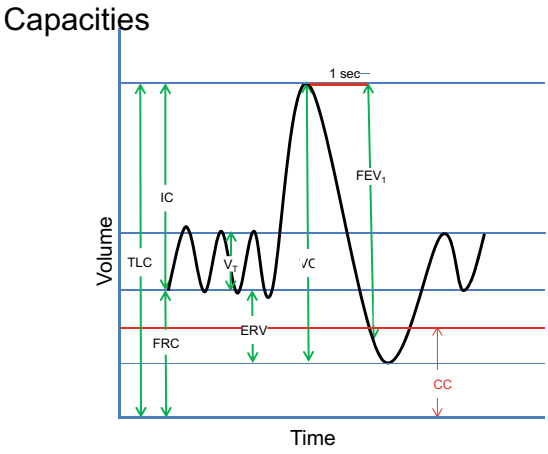


Fig. 1.1 Spirometry showing lung volumes and capacities. Total lung capacity = TLC, IC = Inspiratory capacity, FRC = Functional residual capacity, VT = Tidal volume, ERV = Expiratory reserve volume, VC = Vital capacity, FEV_1 = Forced expiratory volume in 1 s, CC = Closing capacity (measured only by gas dilution techniques). Reprinted with permission from Sarnaik AP, Heidemann S and Clark JA, Nelson Textbook of Pediatrics, 20th Edition, Kliegman, St. Geme et al. Editors, Elsevier 2016

thoracic gas volume by plethysmography or by helium dilution method. FRC acts as a reservoir for gas exchange between the alveoli and the pulmonary capillary blood throughout respiration. Diseases that decrease lung compliance and lower FRC can have profound effects on oxygenation. Positive end-expiratory pressure (PEEP) helps maintain end-expiratory volume and improve oxygenation. *Residual volume* (RV) is the volume of gas remaining in the lung after a maximal forced exhalation. The difference between FRC and RV is the *expiratory reserve volume*. *Inspiratory capacity* (IC) is the volume that can be inspired from FRC after a maximal inspiration from a normal exhalation and *total lung capacity* is the total volume of gas in the lung at maximum inspiration. Closing capacity (CC) is volume of gas in the lung during exhalation when the dependent airways start to close. Closing capacity can only be measured by specific gas dilution techniques and not by spirometry. In healthy children and adults, CC is well below the FRC, meaning that all the airways remain open during tidal respiration. In intrapulmonary obstructive diseases and even in healthy neonates, dependent airways start to close during tidal exhalation before reaching FRC. When CC is greater than FRC, the alveolar ventilation moves towards the nondependent, less perfused areas, away from dependent and better perfused areas, resulting in V/Q mismatch and a lower PaO_2. This also results in some amount of air trapping.

1.2 Pressure

In regards to pulmonary mechanics, pressure is generally described in relation to atmosphere which is considered to be 0 cm H_2O. During spontaneous breathing, inspiration results from negative pressure in the pleural space and alveoli drawing air from the atmosphere, while during positive pressure breathing air is pushed into the alveoli from a higher pressure source. There is a lack of consistency with terms and symbols used to describe reference pressures and pressure gradients. For the purpose of this discussion, we will use the following terminology (Fig. 1.2).

Proximal airway pressure (P_{AW}) is measured at the mouth during spontaneous breathing, inside the ventilator, at the patient-support device interface during non-invasive breathing support or in the hub of the endotracheal tube during invasive mechanical ventilation. When measured at the mouth during spontaneous respiration, it is same as the atmospheric pressure (P_{ATM}) or body surface pressure (P_B) which is referred to as 0 cm H_2O. During mechanical ventilation, P_{AW} is usually measured in the ventilator via a pressure transducer in various phases of respiratory cycle. Alveolar pressure (P_{ALV}) is inferred by inspiratory and expiratory occlusion techniques, allowing the P_{ALV} to equilibrate with the P_{AW} by accomplishing a "no flow" state and measuring pressure at the proximal airway. A no flow state assumes equalization of pressure at both ends of the system. Intrapleural pressure (P_{PL}) is not directly measured in clinical practice. Instead, it is inferred by measuring esophageal pressure (P_{ES}) by a balloon placed in distal esophagus.

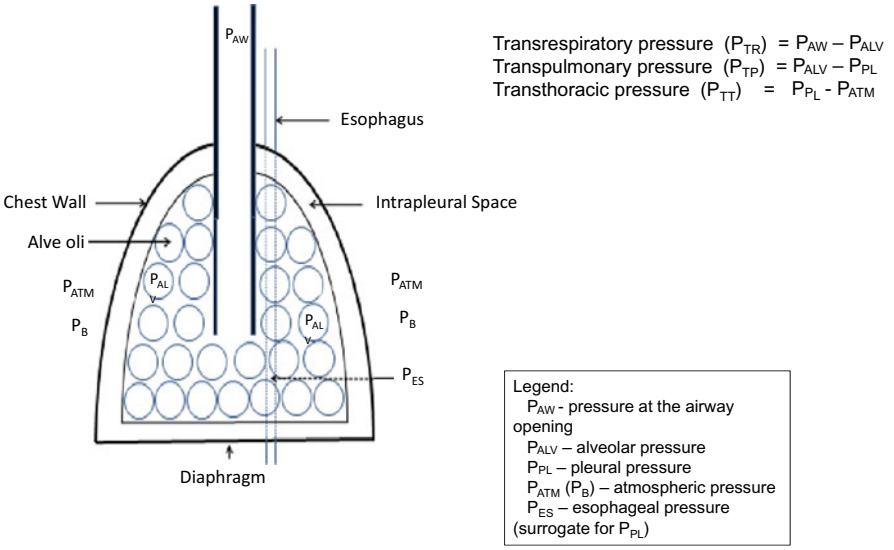


Fig. 1.2 Schematic presentation of various sites at which reference pressures are measured. P_{ATM} or P_B = atmospheric or body surface pressure, P_{AW} = proximal airway pressure, P_{ALV} = alveolar pressure, P_{PL} = intrapleural pressure, P_{ES} = esophageal pressure (used as a surrogate for P_{PL})

1.3 Pressure Gradients

Transrespiratory pressure is the pressure difference between P_{AW} and P_{ALV}. Transthoracic pressure ($P_{ATM} - P_{PL}$) is the pressure difference that thoracic cage is subjected to throughout the respiratory cycle. P_{ES} is used as a surrogate measure of P_{PL}. Transpulmonary pressure ($P_{ALV} - P_{PL}$) is the pressure difference between the alveolar pressure and the pleural pressure and is indicative of the pressure responsible for maintaining alveolar inflation. It reflects the stress the alveoli are exposed to during inflation and deflation with mechanical ventilation. Measurement of transpulmonary and transthoracic pressures allow the partitioning of the combined lung-thorax mechanics into separate chest wall and alveolar components. Trans-airway pressure ($P_{AW} - P_{ALV}$) denotes the pressure difference that influences air movement (flow) across the airways. It is used to calculate airway resistance (pressure/flow).

1.4 Surface Tension

Alveolar surface is lined with a liquid film creating an air-fluid interface for gas exchange. Alveoli are connected to each other and the atmosphere via airways. The pressure required to keep an alveolus open is governed by Laplace's law which is expressed as:

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

where P is the pressure required to inflate the alveolus, T is the surface tension at the air-fluid interface, and r is the radius. Pressure needed to keep the alveolus open is greater, with higher surface tension and smaller radius. If surface tension remains the same, smaller alveoli will tend to collapse and empty into larger alveoli resulting in atelectasis. Pulmonary surfactant is produced by type II alveolar cells and forms the lining of alveolar air interface. There are two major functions of surfactant. Surfactant is necessary to decrease the surface tension thereby requiring less pressure (critical opening pressure) for alveolar inflation. Surfactant also decreases the surface tension of smaller alveoli to a greater extent compared to the larger ones. Because the concentration of surfactant is greater in smaller alveoli compared to larger alveoli, the surface tension is decreased to a greater extent thus equalizing the pressure in alveoli of different sizes (Fig. 1.3).

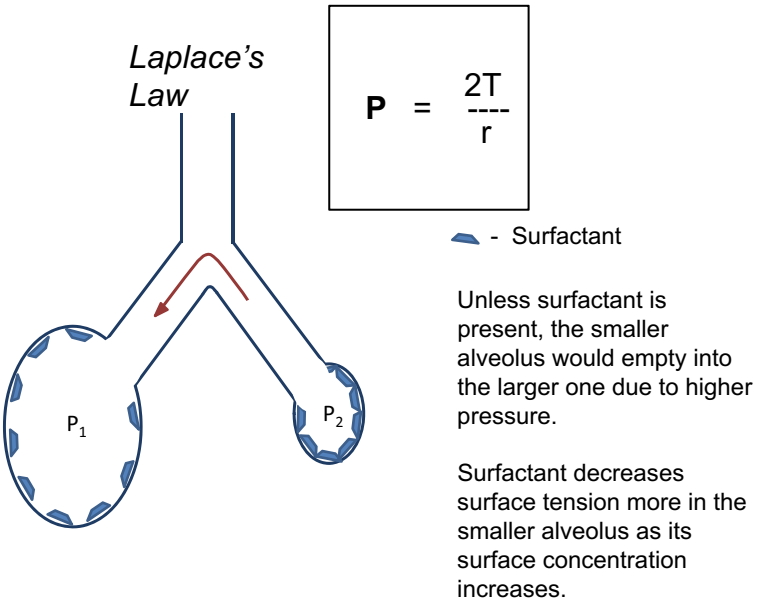


Fig. 1.3 Pressure generated in a smaller alveolus (P_2) is greater than that in a larger alveolus (P_1) with a tendency of the smaller alveolus to empty into the larger one. Surfactant, in general, lowers the surface tension. Being more concentrated in a smaller alveolus, surfactant lowers the surface tension to a greater extent allowing alveoli of different sizes to remain open and in communication with each other.

1.5 Elastance and Compliance

Elastance is the property of a substance to return to its original state when the deforming stress (e.g. pressure) is removed. Pulmonary elastance is determined by two factors: elastin in elastic fibers in the connective tissue of the lungs including the airways and surface tension in the alveoli. Elastance is decreased with loss of elastin and increased with increased surface tension or accumulation of fluid and inflammatory material. Elastance of the chest wall is determined by the stiffness and the integrity of its skeletal components and, strength and tone of the musculature.

$$E = \frac{\Delta P}{\Delta V}$$

where E = Elastance, P = Pressure, and V = Volume. Elastic recoil refers to the rapidity and force (pressure) with which a substance returns to its original state when the deforming stress is removed. Compliance, which is the inverse of elastance, refers to the distensibility or stretch-ability of a substance when subjected to a deforming stress.

$$C = \frac{1}{E} = \frac{\Delta V}{\Delta P}$$

Specific compliance Since small lungs will have a smaller volume change when subjected to the same amount of pressure change, compliance is sometimes corrected to lung volume (usually functional residual capacity) to more accurately describe the structural properties of tissues. As a matter of convenience, compliance is sometimes corrected for weight or height of the patient to reflect the effect of size of the lung. This is referred to as specific compliance.

During normal spontaneous breathing, lungs and chest wall recoil in different directions during tidal respiration. Recoil pressures of the lungs and the chest wall refer to their respective pressures generated (in opposite directions) as they tend to return to their passive volume at 0 cm H_2O atmospheric pressure. Chest wall tends to recoil to a higher volume during tidal respiration while the lungs tend to recoil towards the lowest volume.

Although lungs and chest wall have their individual elastance and compliance properties, they need to be considered together since they are connected by pleural space which transmits recoil forces generated by one to the other. Individual elastic recoil pressures of chest wall and lung are represented schematically at various lung volumes corresponding to a percentage of total lung capacity (Fig. 1.4). At any

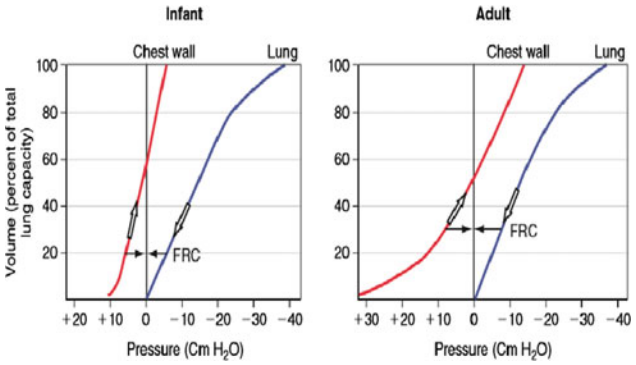


Fig. 1.4 Interaction between chest wall and lung recoil pressures in infants compared to adults. The lower recoil pressure of the chest wall in infants favors a lower FRC in infants. **FRC** – Functional Residual Capacity (Reprinted with permission from Sarnaik AP, Heidemann S and Clark JA, *Nelson Textbook of Pediatrics*, 20th Edition, Kliegman, St. Geme et al. Editors, Elsevier 2016)

volume, both the lung and the chest wall recoil to their passive volumes where their recoil pressure will be 0 cm H_2O. When corrected for volume, an infant's lungs exhibit remarkably similar elastance (and compliance) for an equivalent % change in volume compared to a healthy adult. The major difference between a neonate and an adult lies in the elastance of the chest wall. Neonatal chest wall has much less elastic recoil compared to an adult chest wall. It generates/requires less pressure (i.e. is more compliant) for a given change in volume. It can be easily understood that the elastic recoil pressure generated by the lung will bring about a greater change in the neonatal chest wall compared to the adult chest wall. The amount of air left in the lung at the end of tidal exhalation is referred to the functional residual capacity (FRC) which serves an important function as a reservoir for gas exchange during exhalation. At FRC the recoil pressures of the chest wall and the lungs are equal and opposite. FRC is also therefore termed as the "rest volume" which is achieved by equal and opposite recoil forces of the lung and the chest wall with no energy expenditure. The actual FRC determined in a spontaneously breathing neonate is considerably higher than what can be expected on the sole basis of respective lung and chest wall recoils. It is closer to what is observed in older children and adults corrected for lung volume. This is because (1) a neonate holds its chest wall in inspiratory position at the end of expiration by sustained tonic activity of the diaphragm and intercostal muscles, (2) increased respiratory rate (decreased time for exhalation) does not allow for complete lung deflation and (3) higher closing capacity which exceeds the volume at which tidal ventilation is occurring.

There are several implications of the lung-chest wall interaction in infants compared to older children. In newborns, the chest wall compliance is 3 to 6 times greater than the lung compliance. By 1 year of age, the chest wall elastance increases sufficiently to maintain FRC at a higher level solely on the basis the respective elastic recoils of the lung and the thoracic cage. In younger infants however, a marked decrease in FRC can occur in certain states: (1) conditions where inspiratory muscle tone is decreased, the chest wall becomes increasingly compliant such as during REM sleep, or with neuromuscular diseases (e.g. myopathies, neuropathies), use of sedatives/anesthesia and muscle relaxants, and CNS depression; (2) increased lung elastance (decreased lung compliance) such as with ARDS, pneumonia, pulmonary edema; and (3) extrathoracic airway obstruction which worsens during inspiration necessitating higher negative intrapleural pressure. In all these instances, the increasingly deformable chest wall retracts inward to a greater extent with a loss of FRC at end expiration and impeding air entry during inspiration. Under general anesthesia, because of the relaxed chest wall muscles, FRC declines by 10–25% in healthy adults, 35–45% in 6–18 year olds and greater than 50% in younger children. Application of PEEP is necessary in such instances to prevent atelectasis and hypoxemia.

1.5.1 Static and Dynamic Compliance

The pressure needed to overcome elastic recoil and move air, is measured once pressure has equilibrated and airflow has stopped. When compliance (ΔV/ΔP) is measured in this manner it is termed static compliance (C_{STAT}). Additional pressure is necessary to overcome resistance when air is flowing. The effect of resistance on compliance can be demonstrated using a pressure–volume plot (Fig. 1.5). The static relationship between pressure and volume is represented by the line A. At any given change in pressure, a corresponding change in volume is achieved, once airflow has stopped. The additional pressure necessary to overcome resistance is represented by the curves B and C when flow is occurring. During air flow, the same change in pressure results in less change in volume depending on the amount of resistance.

The ΔV/ΔP relationship during flow is termed dynamic compliance (C_{DYN}). The C_{DYN} for curve C is lower than for curve B because of increased resistance. Therefore, the difference between C_{DYN} and C_{STAT} represents the degree of resistance. Clinically, the difference between static and dynamic compliances can be measured during mechanical ventilation. When patients are receiving a set tidal volume using constant flow (volume control mode), the difference between peak

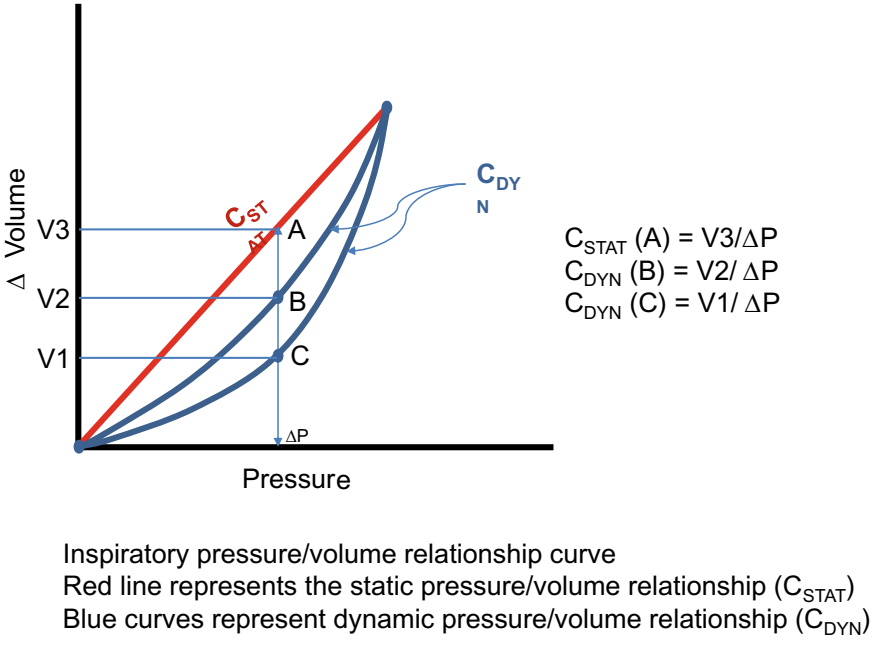


Fig. 1.5 Inspiratory pressure–volume (PV) curves. The red line (A) represents PV relationship during no-flow (static) state. The blue lines (B and C) represent PV curves while flow (dynamic) is occurring. Static compliance (C_{STAT}) and dynamic compliance (C_{DYN}) are calculated at a given ΔP. C_{STAT} (A) > C_{DYN} (B) > C_{DYN} (C)

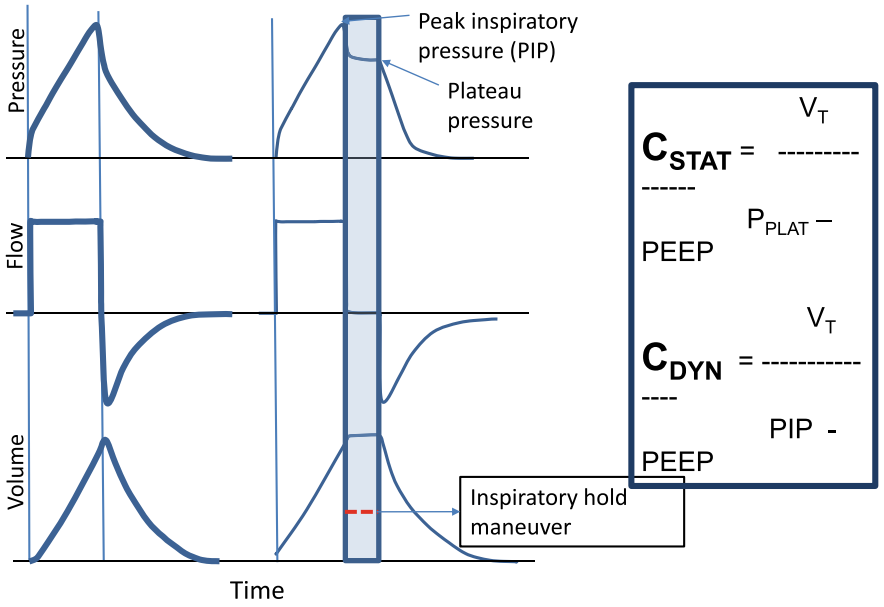


Fig. 1.6 Time relationships are shown for pressure, flow and volume in a volume-controlled ventilation with constant flow. Inspiratory hold is applied after peak pressure (PIP) is reached to allow pressure equilibration to occur between P_{AW} and P_{ALV} resulting in a plateau pressure (P_{PLAT}) which is lower than PIP as resistive forces are overcome

pressure and the plateau pressure obtained using an inspiratory hold maneuver can give an estimate of the airflow resistance (Fig. 1.6).

C_{DYN} can be calculated as the tidal volume divided by the difference between the peak inspiratory pressure and the end-expiratory pressure (Fig. 1.6). C_{STAT} is calculated as the tidal volume divided by the difference between the plateau pressure and end-expiratory pressure (Fig. 1.6). During volume controlled ventilation, P_{PLAT} is always lower than PIP and therefore C_{STAT} is always lower than C_{DYN}, and the degree of difference is dependent of the degree of airway obstruction.

1.5.2 Frequency Dependence of Compliance

Dynamic compliance (C_{DYN}) takes into account both the resistance (when flow is maximum) and the compliance (when flow is zero) of the respiratory system. Unlike C_{STAT}, which is relatively constant and a reflection of structural properties of the lung, C_{DYN} takes into account the flow resistive properties of the airways as well as the structural properties. Since the pressure required is a product of flow and resistance, an increase in either the flow or the resistance will require a greater pressure when considering the dynamic compliance. An increase in respiratory

frequency will decrease the amount of time provided for inflation and deflation to occur and necessitate an increase in flow. The resultant increase in flow resistive property will require a greater pressure to deliver the tidal volume and thus a decrease in C_{DYN}. This is termed frequency dependence of compliance; C_{DYN} decreases with increase in respiratory frequency. In diseases of increased resistance (prolonged time constant), C_{DYN} decreases markedly as respiratory frequency is increased.

1.6 Resistance

For air to flow across the airways, some force (pressure) is required to overcome opposing forces (resistance) such as inertia and friction. In the context of air movement from the mouth into the alveoli, the responsible pressure is termed the transrespiratory pressure gradient (P_{AW} –P_{ALV}). In a spontaneously breathing patient the pressure at mouth or proximal airway is same as the atmospheric pressure whereas with mechanically ventilated patient the proximal airway pressure is pressure at the patient-machine interface. Air flows from a higher pressure to a lower pressure both during inspiration and expiration. When the pressures at two ends are equal, flow ceases. By the same token, when airway is occluded stopping the flow, pressure is presumed to have equilibrated after a period of time. These airway occlusion techniques are utilized at various phases of respiration to estimate alveolar pressure measured at the proximal airway which is readily available for pressure measurement. Resistance is calculated as transrespiratory pressure gradient required generating a given amount of flow (volume per time) and expressed conventionally as cm H_2O/L/sec. Two of the important determinants of resistance to airflow are: (a) airway diameter and (b) nature of the flow, laminar or turbulent.

Laminar versus Turbulent flow: When gas molecules travel in a straight direction, the flow is referred to as being laminar. At higher velocities (distance/time), such as would occur when same amount of flow (volume/time) is pushed through a narrowed airway, the movement of gas molecules becomes chaotic thus resulting in turbulence.

Laminar flow Turbulent flow

Whether the flow is laminar or turbulent depends upon density, viscosity and velocity of gas and the diameter of the airway. When airflow is laminar, resistance is governed by Poiseuille's law:

$$R = \frac{8nL}{\pi r^4}$$

R is resistance, l is length, η is viscosity, and r is the radius. The practical implication of pressure-flow relationship is that airway resistance is inversely proportional to its radius raised to the 4th power. If the airway lumen is decreased in half (1/2), the resistance increases 16-fold. A flow change from laminar to turbulent occurs when Reynold's number exceeds 2000. Reynold's number (Re) is a dimensionless entity represented as:

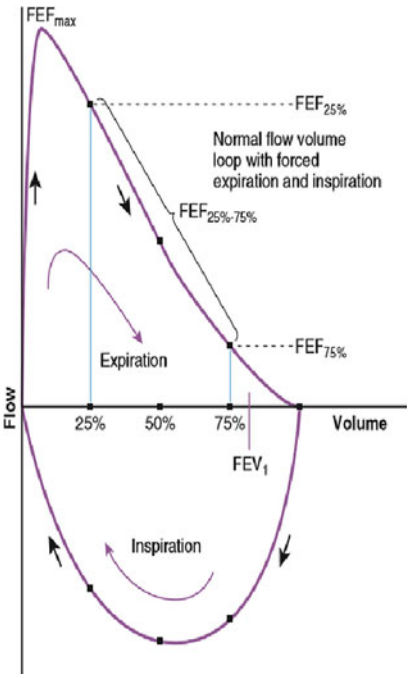
$$\text{Re} = (\text{Diameter} \times \text{Velocity} \times \text{Density}) \div \text{Viscosity}$$

Resistance to turbulent flow is much greater than to laminar flow. In clinical situations, the most effective way of decreasing the Reynold's number is to decrease the density of inspired gas. For this purpose, helium is used to replace nitrogen to promote laminar flow. Helium is about 7 times less dense and slightly more (1.1X) viscous than nitrogen. For helium to be effective for this purpose, it needs to be present to a sufficient degree. It is generally believed that for Helium–oxygen mixture (Heliox) to effectively reduce resistance, at least 50–60% of the mixture needs to be comprised of helium. This means patients requiring more than 50% oxygen may not benefit from Heliox.

Resistance to airflow is different during inspiration and expiration. In normal circumstance, expiratory resistance is higher than inspiratory resistance. This is because the intrathoracic airways expand during inspiration as they are subjected to more negative pleural pressure from the outside in spontaneous breathing and positive pressure from the inside in mechanical ventilation. In intrathoracic airway obstruction (asthma, bronchiolitis, vascular ring etc.) this discrepancy increases as expiratory resistance increases exponentially due to airway compression by excessively positive pleural pressure. In extrathoracic airway obstruction (subglottic stenosis, vocal cord paralysis etc.), the inspiratory resistance can exceed the expiratory resistance as the airway outside the thorax collapses because of excessively increased intraluminal negative pressure.

1.7 Flow/Volume Relationships

Flow/volume relationships curves are clinically useful tools for demonstrating the effect changes in pulmonary mechanics have on volumes and gas flow (Fig. 1.7). These curves are generated with spirometry machines and can be used in both the outpatient setting well as the bedside. Typically, a maximal inspiration is followed by maximal forced exhalation, generating a flow/volume loop. Forced vital capacity (FVC) is the total volume exhaled during this maneuver. Forced expiratory volume during the first second of exhalation is termed FEV1. Decreases in FVC and FEV1 result from decreased lung compliance, increased airway resistance and decreased



A normal flow/volume loop. Performed by maximal inspiration followed by maximal forced exhalation to completion.
FEF$_{MAX}$ is synonymous with peak expiratory flow rate (PEFR) and represents the maximum expiratory flow rate during exhalation. This occurs soon after the start of forced exhalation.
FEF$_{25\%-75\%}$ represents the mean flow between 25% and 75% total expiratory volume. Also referred to as mid maximum expiratory flow rate (MMEFR).
FEV$_1$ is the volume of expired gas in the first second of expiration.

Fig. 1.7 Flow-volume loop created by maximum inhalation followed by forced maximum exhalation

respiratory muscle strength. The maximum flow occurs in the first phase of forced exhalation and is referred to as FEF_{max} (also referred to as peak flow). It is effort dependent but also a marker of airway obstruction. The volume exhaled between 25 and 75% of the expiratory volume (FEF 25–75%) is relatively effort independent. The reason for this is that a higher intrathoracic pressure results in narrowing of intrathoracic airway preventing further increase in flow.

A decrease in $FEF_{25–75\%}$ is indicative of intrathoracic airway obstruction such as in asthma (Fig. 1.8). The shape of the expiratory curve gives clues to disease pathophysiology, as in obstructive disease, where the mid-expiratory curve may be increasingly concave. In restrictive lung and chest wall diseases, all the lung volumes and capacities are decreased without appreciable decreases in flow rates.

Intrapulmonary Airway Obstruction (A): note the decrease in **FEF_{MAX}** and **$FEF_{25\%-75\%}$** and the concavity of the mid-expiratory curve.

Restrictive disorder (B): Note the more vertical and narrow shape. **FVC** is decreased but flow rates are relatively less affected.

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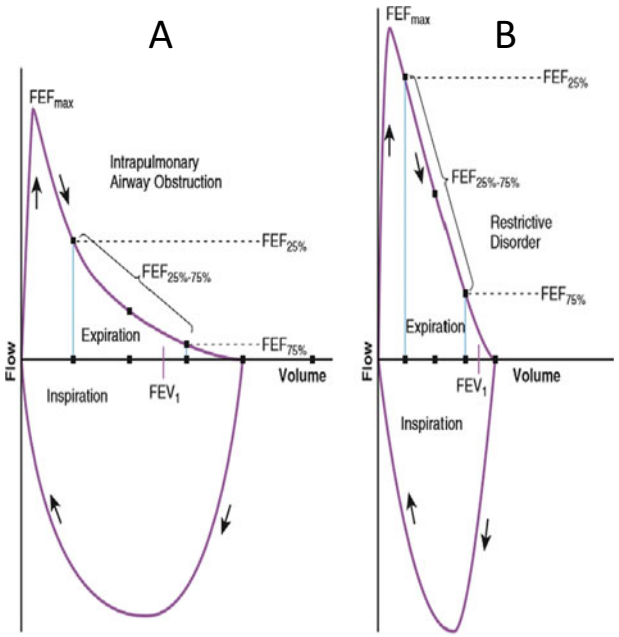

Fig. 1.8 Flow volume loops in intrapulmonary obstructive lung disease (**a**) and restrictive disorders (**b**)

1.8 Equal Pressure Point (EPP)

When intrathoracic airway pressure is increased during exhalation (either by forced voluntary exhalation or in intrathoracic airway obstruction), the pressure must dissipate along the airway to reach the reference atmospheric pressure of 0 cm H_2O or the positive end expiratory pressure set in the mechanical device. The site at which the intraluminal pressure equals pleural pressure is termed the equal pressure point (EPP).

The significance of EPP is that the pressure in the intrathoracic airway proximal to this point (downstream) is less than intrapleural pressure and therefore subject to collapse depending on the magnitude of the pressure difference and stiffness/softness of its wall. With intrathoracic airway obstruction, the EPP is shifted distally towards the alveolus, causing a greater length of airway to collapse above (Fig. 1.9). Softer infantile airways are more susceptible to change in diameter when subjected to increased pressure. Marked dynamic changes in intrathoracic airway diameter during inspiration and exhalation in young infants above EPP are often termed collapsible trachea. Tracheal collapse is often a result of airway obstruction and even contributes to its severity but it is rarely the primary abnormality.

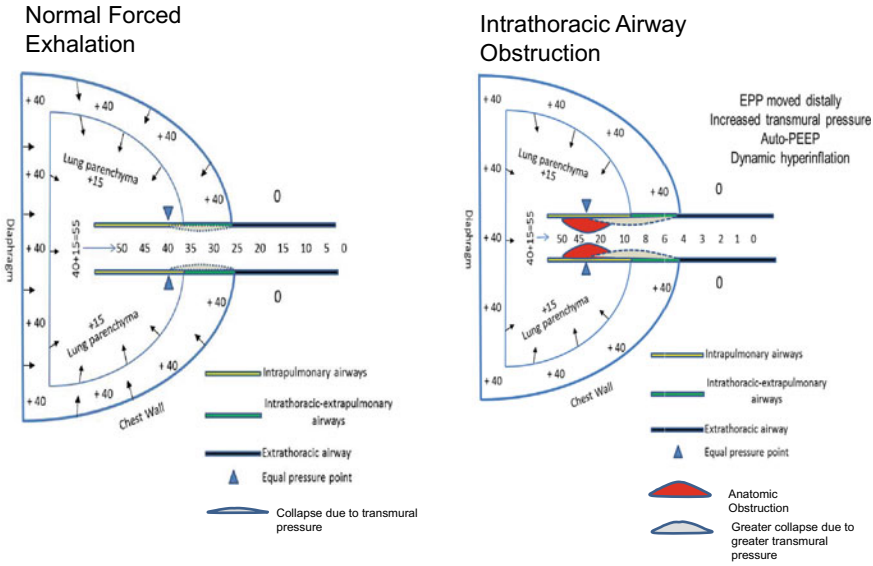

Fig. 1.9 Equal pressure point (EPP) is a site at which intrathoracic and intraluminal pressures during exhalation are equal. Proximal to EPP (downstream), intrathoracic pressure exceeds intraluminal pressure resulting in airway collapse. EPP is displaced distally in intrathoracic airway obstruction, and the magnitude of difference between intrathoracic and intraluminal pressures is increased resulting in greater airway collapse

Suggested Readings

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Chapter 2
Physiology of Inflation and Deflation

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The process of breathing, spontaneous or mechanical, involves the physical movement of air in and out of the lungs. Interaction of various physical factors is involved in the way this process occurs physiologically. It is important to understand these factors as they relate to diagnosis and management of lung disease.

2.1 Equation of Motion

A pressure gradient (Δ pressure) is required to move air in and out of the lung. In normal spontaneous respiration, air is drawn from the atmosphere into the alveoli because of negative intrapleural pressure generated by contraction of the diaphragm and intercostal muscles during inspiration and released from alveoli into the atmosphere during expiration by pressure generated from elastic recoil of the lung. During mechanical ventilation, gas flows into the lungs from positive pressure created by the ventilator during inspiration and exhalation results from alveolar pressure generated by elastic recoil of the lung and chest wall.

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Regardless of the site where it is generated, the pressure necessary to move air is expended for two opposing mechanical factors: (1) *elastance* (inverse of compliance) and (2) *resistance* (Fig. 2.1). Major component of resistance is experienced in generation of airflow across the airways and a minor component is from frictional resistance of tissues. Pressure to overcome elastance is measured by determining the change in volume (Δ volume) after pressure has equilibrated at both ends and flow has ceased. Alveolar pressure is determined in the proximal airway by performing the inspiratory occlusion technique. This means that both the Δ volume and the Δ pressure are determined when pressure has equilibrated throughout and airflow has ceased. Resistance on the other hand is experienced only when airflow is occurring. Thus, the pressure to overcome resistive forces is measured by determining the Δ pressure applied at the source and the flow that results from this. When compliance is measured at a point where there is no flow, it is referred to as static compliance (C_{STAT}). When measured while the flow is occurring, it is referred to as dynamic compliance (C_{DYN}).

2.2 Time Constant

For airflow to occur, a pressure gradient has to be created from one end to the other (proximal airway and the alveoli). Flow will continue as long as the pressure gradient remains between the two ends. When pressure equilibrates at two ends, flow ceases. The equilibration of pressure does not occur instantaneously. It takes some time for pressure to equilibrate at two ends. The time required for pressure

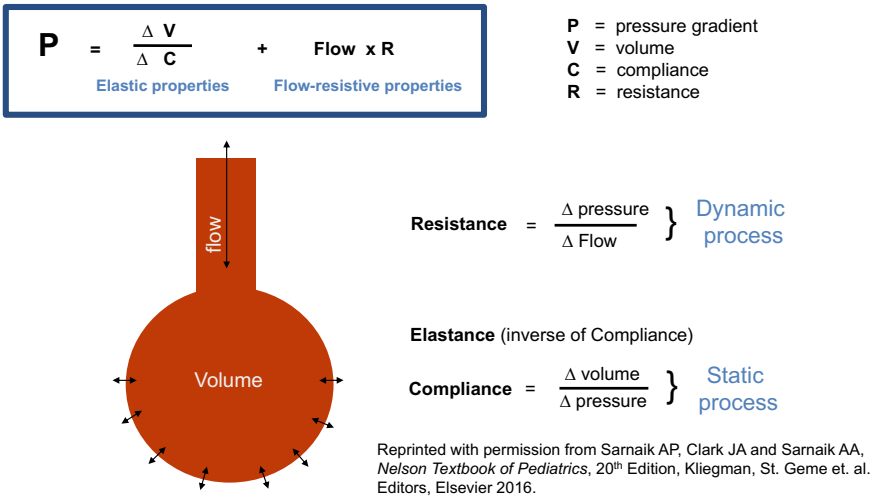

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Fig. 2.1 Equation of motion. Pressure required to move air in and out of the lung is to overcome Resistance (dynamic process) and Elastance (static process)

gradient depends on two variables: (1) compliance and (2) resistance. When compliance is low (meaning elastance is high), the elastic recoil pressure of the lung is increased. During inspiration, inflow of air is opposed by high lung recoil (decreased compliance) and during exhalation; outflow of air is aided by it. This results in quicker attainment of pressure and equilibration volume with cessation of flow in a relatively short time. On the other hand, when airway resistance is increased, longer time is required for pressure/volume equilibration and cessation of air flow to occur. Time constant is a reflection of the time necessary for pressure/volume equilibration to occur and airflow to cease. Thus, the required time is directly proportional to both compliance and resistance. Greater the compliance and resistance, longer the time needed and vice versa. Indeed, time constant is calculated as:

$$\tau(TimeConstant) = Compliance \times Resistance$$

$$\tau = \frac{\Delta V}{\Delta P} \times \frac{\Delta P}{Flow}$$

$$\tau(\mathrm{s}) = \frac{--mL}{--cms} \times \frac{--cms}{--mL/s}$$

Thus, time constant is appropriately represented as time (Fig. 2.2).

It takes one time constant for 63%, two time constants for 86%, 3 time constants for 95% and 5 time constants for almost complete pressure or volume equilibration to occur. Since time constant is a product of compliance and resistance, patients with increased airway resistance require greater time during inspiration and

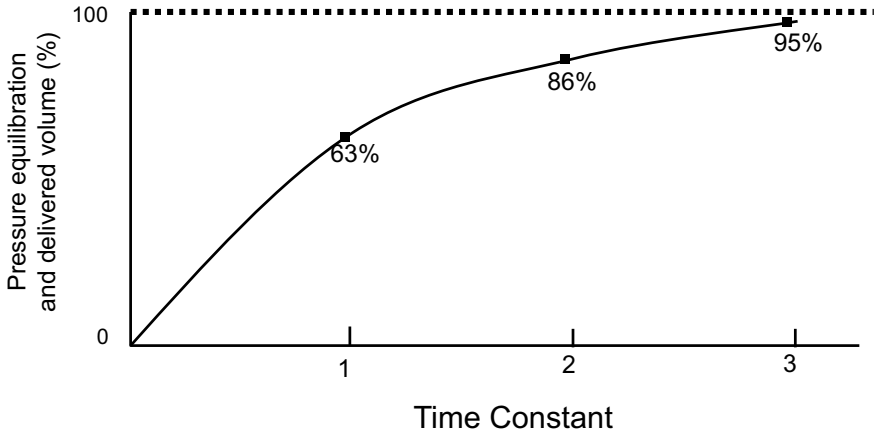


Fig. 2.2 The time required for % of pressure equilibration (and therefore the volume delivery) depends on the time constant of a given system

expiration for pressure and volume equilibration to occur and airflow to cease. Conversely, in patients with diseases of decreased compliance, pressure and volume equilibration occurs quicker. Airways expand during inspiration and narrow during exhalation. Thus, expiratory time constant, because of increased airway resistance is greater than inspiratory time constant. This discrepancy becomes more pronounced in diseases of increased airway resistance (asthma, vascular ring etc.) where expiratory time constant is markedly increased to the point pressure equilibration at the end of expiration does not occur resulting in hyperinflation and auto-PEEP (see below).

The effects of compliance and resistance on time constant are presented in Fig. 2.3. Let's consider that based on compliance and resistance of a normal lung the time constant is X seconds. This would mean that if a pressure of 10 cm H_2O is applied at one end it would take 3X seconds for the other end to receive 9.5 cm H_2O (95% of the driving pressure). The expiratory time constant will be greater than inspiratory time constant because airway resistance is greater in exhalation as they become narrower compared to during inspiration. In diseases with decreased compliance, the time constant will be less than X seconds. Although the volume delivered will be less than in a normal lung, the pressure equilibration is quicker. The inspiratory and expiratory time constants are closer to each other because of greater lung recoil pressure. In diseases of increased airway resistance, the time constant is greater than X seconds as the proximal pressure takes more time to

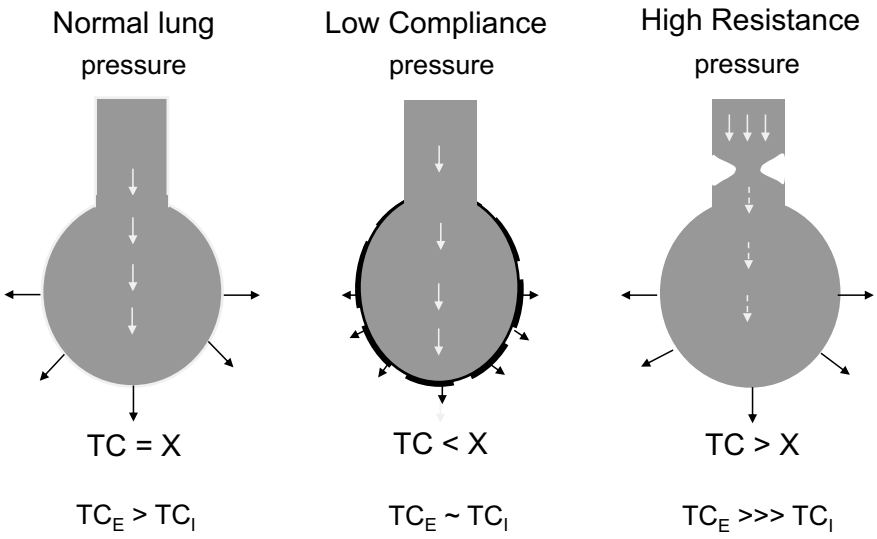


Fig. 2.3 Effect of decreased compliance and increased resistance on time constant (TC). Normally, TC is longer during exhalation as airways get narrower compared to inhalation. Diseases with decreased compliance have decreased TC with expiratory TC (TC_E) getting closer to inspiratory TC (TC_I). Diseases of airway obstruction have prolonged TC with TC_E far exceeding TC_I

overcome airway resistance. In intrathoracic airway obstruction which gets worse during exhalation, the expiratory time constant is much more increased compared to the inspiratory time constant.

Even though a disease can be classified as that of increased resistance (e.g. asthma) or decreased compliance (e.g. ARDS), most lung diseases are often heterogeneous in nature.

Normal lung units are interspersed with units with prolonged time constants (increased resistance) and those with short time constants (decreased compliance). The effect of time on the delivered volume after application of pressure is shown in Fig. 2.4. The units with short time constants fill up (or empty) quickly, with negligible change in volume as time is increased from A to B. The units with increased time constants however fill up (or empty) much slower with greater volume change with time B compared to time A. Consideration of time constant is extremely important when choosing respiratory rate and I:E ratio during mechanical ventilation.

2.2.1 Auto-PEEP and Dynamic Hyperinflation

Auto-PEEP and dynamic hyperinflation exist when exhalation is incomplete and the alveolar pressure has not had sufficient time to equilibrate with atmospheric (or ventilator) pressure during exhalation. As a result, the lung volume is increased above the potential FRC when lung recoil is complete. This occurs in two situations: (1) in patients with airway obstruction such as asthma, time constant is

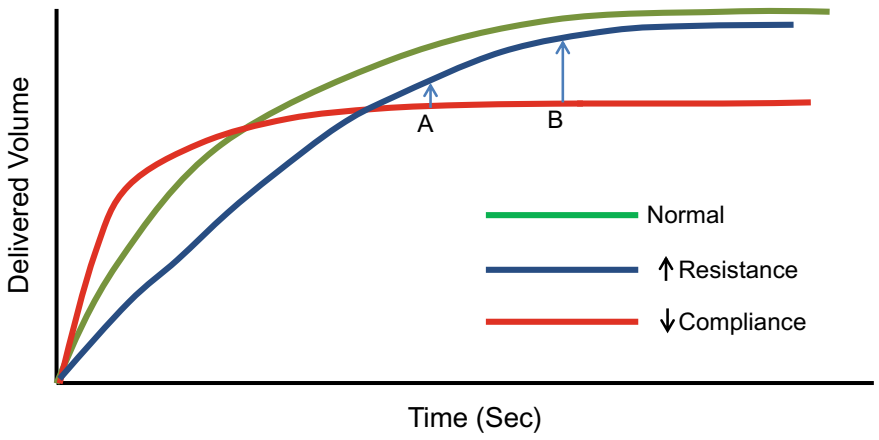


Fig. 2.4 Change in volume delivery in lung units with different time constants. Increasing time from A to B will result in greater volume change in lung units with prolonged time constant (increased resistance) compared to the little change in volume in those units with short time constant (decreased compliance) where pressure equilibration has already occurred

prolonged, much more so during exhalation, preventing complete alveolar emptying. Inspiration occurs either spontaneously or is delivered mechanically before alveolar pressure approximates proximal airway pressure at end expiration. This is termed auto-PEEP and (2) at high respiratory rates, the decrease in expiratory time is not sufficient for complete alveolar emptying to occur. This is referred to as dynamic hyperinflation. Neonates, with their high respiratory rates experience dynamic hyperinflation. Dynamic hyperinflation also results during exercise where both tidal volume and respiratory frequency are increased.

2.3 Work of Breathing

2.3.1 Pressure–Volume Work

In physics, work is defined as the product of force and distance. In the context of respiratory mechanics, work of breathing (WOB) is defined as the product of pressure and volume. It represents the energy required to move air in and out of the lungs. In spontaneous breathing, the work is done by the patient whereas in controlled mandatory breaths, the work is done by the ventilator. Except in situations when expiration is active (obstructive lung disease and forced expiration), WOB is performed during inspiration while the exhalation is passive and the work is accomplished by elastic recoil of the lung. In obstructive lung disease, the patient has to perform expiratory work by creating positive intrapleural pressure by diaphragmatic and intercostal contraction. Calculation of WOB requires consideration of pressure–volume relationship. As stated in equation of motion, one component of pressure required to effect a change in lung volume is to overcome its elastance and the other is to overcome its flow-resistance properties. In the Fig. 2.5, where spontaneous respiration is presented, the red line represents the static pressure volume relationship when there is no flow. Area covered by ACDA represents the inspiratory elastic work (W_{ELAST}) whereas the area covered by ABCA represents the work that represents the flow-resistive work (W_{RESIST}). The total WOB for a given breath is the sum of W_{ELAST} and W_{RESIST}. Total WOB/min is WOB for each breath X respiratory rate. As tidal volume is increased, W_{ELAST} increases since greater amount of volume is moved at higher pressure. W_{RESIST} on the other hand is greatest at maximum flow. At faster respiratory rates, there is less time for air movement to occur. Therefore, air needs to be moved at a higher flow rate. Thus, W_{RESIST} increases at higher respiratory rates. In health as well as in disease, a given minute alveolar ventilation [(Tidal volume—Dead space) X Respiratory rate] is accomplished at a combination of tidal volume and respiratory rate that necessitates the least amount of energy expenditure. Young infants have a larger W_{ELAST} than W_{RESIST} compared to older children and adults. This is not because their lungs have greater elastic recoil (less compliance), but because their chest wall is more compliant and it tends to retract inwards in response to negative intrapleural pressure

during inspiration making lung inflation more difficult. The total WOB is lowest at a rate of 35–40/min for neonates and 14–16/min for older children and adults.

W_{ELAST} increases disproportionately in diseases with decreased compliance and W_{RESIST} increases in diseases with increased airway resistance. Respirations are therefore shallow (low VT) and rapid in diseases of low compliance and deep and relatively slow (decreased flow rate) in diseases of increased resistance in order to minimize energy expenditure. In healthy children, the energy cost of WOB is only approximately 2% of total body expenditure. In children with chronic lung disease, WOB may contribute to as much as 40% of total energy expenditure.

2.4 Airway Dynamics in Health and Disease

Airways in infants are much more compliant compared to older children and adults resulting in greater changes in airway diameter when subjected to similar transmural pressure changes. To understand the phasic dynamic changes during the respiratory cycle, the airway can be divided into 3 anatomic parts: the extra-thoracic airway from the nose to thoracic inlet, the intrathoracic-extrapulmonary airway from the thoracic inlet to the main stem bronchi, and intrathoracic airway which is embedded in the lung parenchyma. Transrespiratory pressure ($P_{AW} - P_{ALV}$) is responsible for air movement. Please note that P_{AW} refers to proximal airway pressure which is same as mouth or atmospheric pressure during spontaneous ventilation and pressure applied to patient-positive pressure interface (ET tube, face

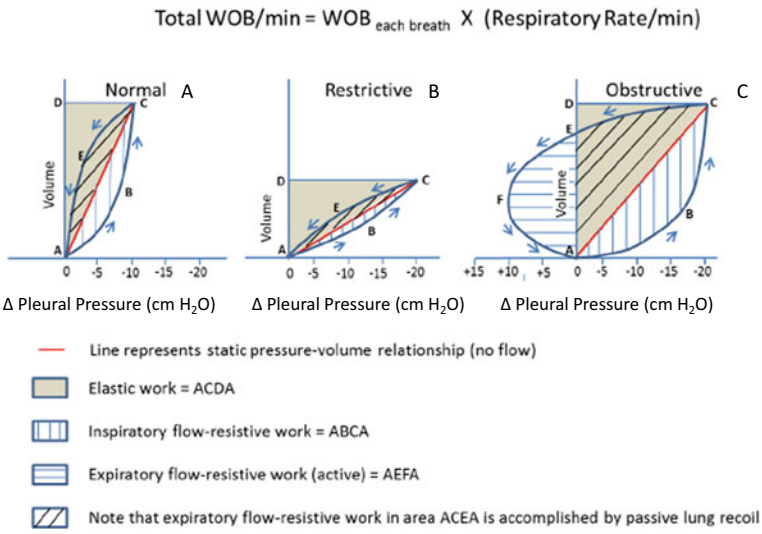
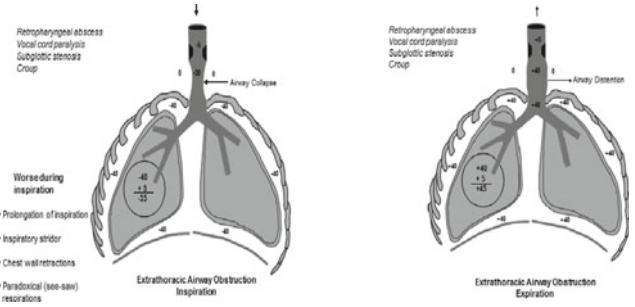


Fig. 2.5 Work of Breathing (WOB) in normal state (**a**), restrictive disease (**b**), and obstructive disease (**c**)

mask, nasal cannula etc.) during mechanical ventilation. P_{ALV} depends on two factors; P_{PL} and recoil pressure of the lung. Lung recoil pressure is greater at higher lung volume and increased elastance (decreased compliance). For the purpose of simplicity, we will assign the value of +5 cm H_2O to lung recoil pressure in order to describe transmural pressures the airways are subjected to during respiration.

During normal spontaneous respirations, intrathoracic airways expand in inspiration because of negative intrapleural pressure, and somewhat narrower during exhalation as they return to the FRC. In diseases characterized by increased airway resistance, a much greater change in intrapleural pressure is required to generate adequate airflow. The transluminal pressure that the walls of the airway are subjected to increase proportionate to the extent the intrapleural pressure is increased. During mechanical ventilation, airways are subjected to positive pressure during inspiration. During exhalation however, it is the positive pressure in the pleural cavity that the alveoli and intrathoracic airways are subjected to. The changes in the size of the airways, which are softer and more compliant, are accentuated in young infants during respiration.

In extra-thoracic (ET) airway obstruction, (retropharyngeal abscess, laryngotracheitis, vocal cord paralysis etc.), most of the increased negative transrespiratory pressure (P_{TR}) during inspiration is transmitted up to the site of obstruction beyond which it is rapidly dissipated. The ET airway below the site of obstruction is subjected to a marked increase in negative intraluminal pressure resulting in collapse. This leads to inspiratory difficulty, prolonged inspiration and inspiratory stridor. Increase in negative intrapleural pressure results in suprasternal, intercostal and subcostal retractions. During exhalation, the increased P_{TR} is again transmitted to the site of obstruction resulting in distension of the ET airway and amelioration of obstruction (Fig. 2.6).

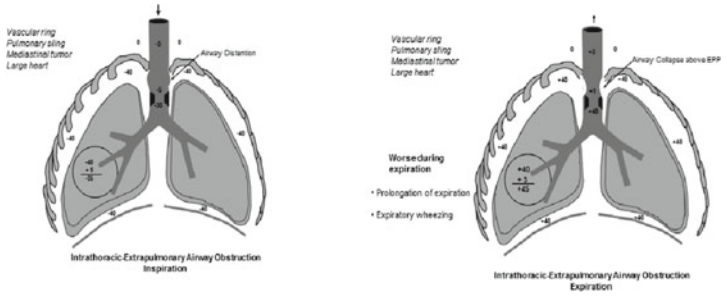


During inspiration, increased negative pleural pressure is transmitted to all airways including the extra-thoracic. This results in collapse of the extra-thoracic airways distal to the site of obstruction. The end result is increased inspiratory resistance and worsening of obstruction.
During exhalation, positive pleural pressure is transmitted to all airways including the extra-thoracic. This results in distention of the airway below the site of obstruction and improvement of symptoms.
Pressures are presented relative to atmospheric pressure (0 cm H_2O). Distal airway pressures are taken as pleural pressure plus lung recoil pressure (arbitrarily taken as +5 cm H_20 for simplicity).

Fig. 2.6 Airways dynamics in extra-thoracic airway obstruction

These symptoms are especially pronounced in newborns and infants with their compliant chest wall and airways. One may observe paradoxical or see-saw respiration as the chest wall retracts inwards and abdomen bulges out due to diaphragmatic descent during inspiration and the converse occurring during exhalation. In obstruction of intrathoracic-extrapulmonary (IT-EP) airways such as vascular ring, pulmonary sling, mediastinal mass etc. the equal pressure point (EPP) is displaced distally and the intrathoracic airway above the obstruction is subjected to an excessive positive intrathoracic pressure (Fig. 2.7).

This results in intrathoracic airway collapse above the EPP, worsening the obstruction leading to the signs and symptoms of expiratory difficulty and wheezing, prolongation of expiration and hyperinflation. During inspiration, there is relatively less obstruction as the IT airway above the obstruction is surrounded by much more negative extraluminal pressure than intraluminal and thus tends to distend with improvement in symptoms. The classic findings of expiratory wheezing in IT-EP obstruction has led to the axiom "all that wheezes is not asthma". In unilateral IT-EP obstruction, such as in foreign body aspiration, the clinical manifestations are predominantly at the site of the lesion. In IP airway obstruction such as with asthma and bronchiolitis, the EPP moves further into the distal airways causing a widespread intrathoracic collapse during expiration resulting in expiratory wheezing, prolonged expiration, air trapping and hyperinflation (Fig. 2.8).



During inspiration, increased negative pleural pressure is transmitted to all structures inside the chest including the airways up to the site of obstruction beyond which it is rapidly dissipated. This results in distension of the intra-thoracic airways proximal to obstruction as it is surrounded by even greater negative intrathoracic pressure. During exhalation, the increased airway pressure rapidly dissipates above the obstruction. There is a collapse of the intrathoracic airway above the obstruction because of markedly increased positive intrathoracic pressure outside the airway making the obstruction worse during exhalation. Equal pressure point (EPP) is the point at which intra and extra luminal pressures during exhalation are equal.
Pressures are presented relative to atmospheric pressure (0 cm H_2O). Distal airway pressures are taken as pleural pressure plus lung recoil pressure (arbitrarily taken as +5 cm H_20 for simplicity).

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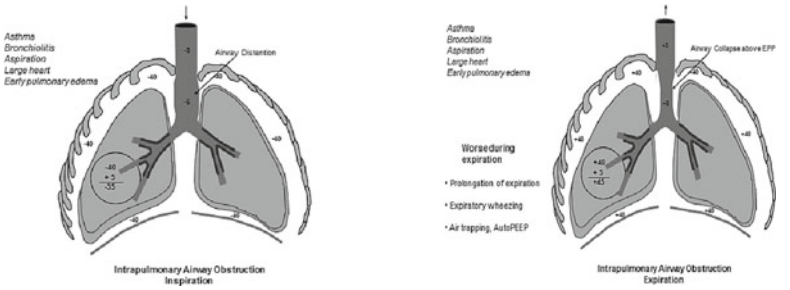
Fig. 2.7 Airway dynamics in intra-thoracic extrapulmonary airway obstruction



During inspiration, increased negative pleural pressure is transmitted to all structures inside the chest including the airways. The intrathoracic extraluminal airway pressure is more negative especially above the site of obstruction resulting in airway distension. During exhalation, the positive intrathoracic pressure rapidly dissipates above the site of obstruction and the equal pressure point moves distally towards the alveoli. The end result is widespread airway collapse and worsening of symptoms. Pressures are presented relative to atmospheric pressure (0 cm H_2O). Distal airway pressures are taken as pleural pressure plus lung recoil pressure (arbitrarily taken as +5 cm H_20 for simplicity).

Fig. 2.8 Airway dynamics in intra-thoracic intrapulmonary airway obstruction

Suggested Readings

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Chapter 3
Gas Exchange

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The main function of the respiratory system is to remove CO_2 from and add O_2 to systemic venous blood brought to the lung. Tissue demands of O_2 supply and CO_2 removal requires the process of matching perfusion and alveolar ventilation (V_A), diffusion of gases across the alveolar capillary membrane, O_2 delivery (DO_2) and consumption (VO_2). These processes are schematically represented in (Fig. 3.1).

3.1 Alveolar Gas Equation

The total pressure of atmosphere (P_{ATM}) at sea level is 760 torr or mm Hg. P_{ATM} is also sometimes expressed in kilopascal unit. 1 kilopascal is approximately 7.5 torr. P_{ATM} decreases progressively at higher altitude (Table 3.1). The total atmospheric pressure is the sum of pressures exerted by each of its component gases. With increasing altitude, P_{ATM} decreases while the fraction of O_2 (FiO_2) remains constant. At temperature of 37°C (98.6°F), and 100% humidity, water vapor exerts pressure of 47 torr regardless of the altitude. Alveolar air is 100% humidified, therefore the inspired gas is also assumed to be fully saturated with water. To subtract the contribution of water vapor, 47 torr is subtracted from the atmospheric pressure to account for the pressure exerted by gases alone. Our atmosphere contains 20.93% (≈21%) oxygen at any altitude. Thus, the fraction of atmosphere comprising of oxygen (FiO_2) is 0.21. Partial pressure of oxygen in inspired gas (PiO_2) is calculated as:

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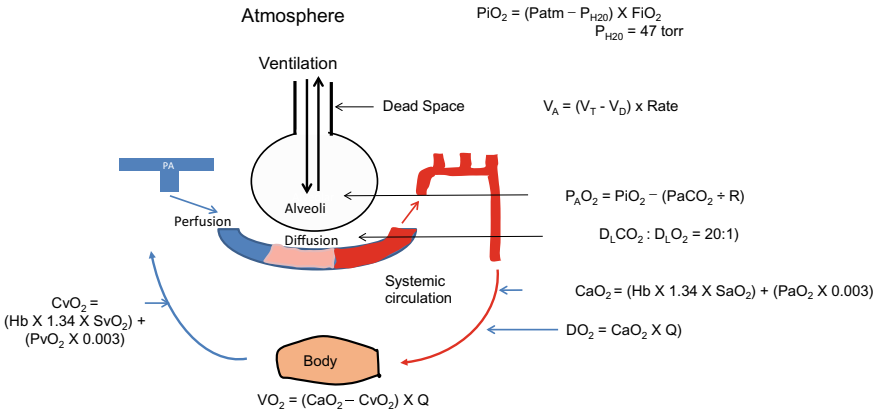

Fig. 3.1 Various factors involved in respiration; Atmospheric composition, Ventilation, Diffusion, Perfusion, Oxygen delivery (DO_2), Oxygen consumption (VO_2), CO_2 production (VCO_2)

Table.3.1 Relationship of barometric pressureand partial pressure of inspired air (PiO_2) when 100% humidified at different altitudes

Altitudes (feet)	P_{ATM}(Torr)	(P_{ATM}-47[P_{H2}o])Torr	O_2%	PiO_2(Torr)
0	760	713	20.93	149
600	747	700	20.93	147
5000	632	585	20.93	123
10,000	523	476	20.93	100
15,000	429	382	20.93	80
18,000[a]	380	333	20.93	70
20,000	349	302	20.93	63
25,000	282	235	20.93	49
30,000	225	178	20.93	37

[a]Highest Village. Modified from Comroe JH. Physiology of Respiration, Year Book Medical Publishers, 2nd ED, Chicago, USA 1974

$$PiO_2 = (P_{atm} - 47) \times FiO_2$$

At sea level, PiO_2 = (760–47) × 0.21 = 149 torr. When breathing 40% O_2 at sea level, PiO_2 = (760 – 47) × 0.4 = 285 torr. At higher altitudes, breathing the same FiO_2 results in a lower PiO_2. In Denver (altitude 5,000 feet, P_{ATM} = 632 mmHg) for example, breathing FiO_2 of 0.21 will result in PiO_2 = (632 – 47) × 0.21 = 123 torr and at FiO_2 of 0.4, it will be (632 – 47) × 0.4 = 234 torr.

3.2 Oxygenation and Ventilation

The amount of air moved in and out of the lungs every minute (V_T x respiratory rate) is termed minute volume. Part of the inspired V_T occupies conducting airways (anatomic dead space) which does not contribute to gas exchange. Still another part of V_T enters alveoli that are not sufficiently perfused (alveolar dead space). Total dead space ($V_D$tot) is the sum of anatomic dead space ($V_D$anat) and alveolar dead space ($V_D$alv). Alveolar ventilation (VA) is calculated as:

$$\dot{V}_A = [V_T - (Vd_{anat} + Vd_{alv})] \times RR$$

where RR is the respiratory rate (Fig. 3.2).

Although dead space is often looked at as moving in bulk, in reality the gas moves at a higher velocity in the center compared to the periphery where frictional resistance slows it down. Thus, alveolar ventilation may be higher than expected because of asymmetric velocity of the inspired gas compared to uniform velocity in a bulk flow model. The relationship of V_T and $V_D$tot is calculated as:

$$\frac{V_D}{V_T} = \frac{\left(P_{A_{CO2}} - P_{\overline{E}_{CO2}}\right)}{P_{A_{CO2}}}$$

where, P_ECO_2 is mixed expired PCO_2. P_ACO_2 is assumed to be same as $PaCO_2$ since there is no A-a CO_2 gradient. To calculate $V_D$alv, $P_{ET}CO_2$ is used to replace mixed P_ECO_2.

$V_D alv/V_T = (PaCO_2 - P_{ET}CO_2) \div PaCO_2$.

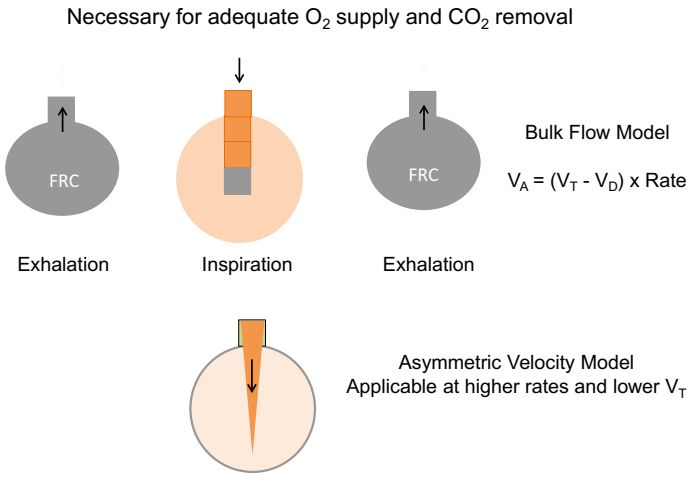

Fig. 3.2 Alveolar ventilation with bulk flow model and asymmetric velocity model

In normal lungs, $P_{ET}CO_2$ should be close to $PaCO_2$ and thus $V_D$alv should be negligible. Increasing difference in $PaCO_2$ and $P_{ET}CO_2$ is indicative of increasing $V_D$alv. Increased $V_D$alv is encountered when pulmonary perfusion is insufficient to match ventilation such as in decreased cardiac output, pulmonary embolism, hypovolemia and excessive PEEP. V_A is inversely proportional to $PaCO_2$. The relationship between V_A and $PaCO_2$ is hyperbolic but at the bedside, in the ranges of $PaCO_2$ commonly seen, it can be assumed to be linear. Therefore, when V_A is doubled, $PaCO_2$ is halved. Conversely when V_A is halved, $PaCO_2$ is doubled. With minor changes during the respiratory cycle the total pressure of all gases in alveoli is very similar to the total pressure of inspired gas. Alveolar gas composition depends on partial pressure of gases in the inspired gas, $PaCO_2$ (assumed to be same as alveolar PCO_2) and respiratory quotient (R). The simplified alveolar air equation is used to calculate the alveolar PO_2 (P_AO_2) as follows:

$$P_AO_2 = PiO_2 - \left(\frac{P_aCO_2}{R}\right)$$

For practical purposes, R is assumed to be 0.8. According to the alveolar air equation, for a given PiO_2, a rise in $PaCO_2$ of 10 torr will result in a decrease in P_AO_2 by $10 \div 0.8 = 10 \times 1.25 = 12.5$ torr. Thus, pure hypoventilation will decrease P_AO_2 with increase in $PaCO_2$ by a factor of 1.25. In a normal person, PiO_2 is about 150 torr. With a $PaCO_2$ of 40 torr, the P_AO_2 will be $150 - (40 \times 1.25)$ torr or $150 - 50 = 100$ torr. An increase in FiO_2 and therefore the PiO_2 will raise P_AO_2 without affecting $PaCO_2$. Dangerous level of hypercarbia may coexist without hypoxia in hypoventilating patients who are breathing supplemental O_2.

The alveolar gas is is exchanged with the systemic venous (pulmonary arterial) blood through the process of diffusion which is influenced by the alveolar capillary barrier and the time available for equilibration. The "arterialized" blood is returned via pulmonary venous circulation to the heart to be pumped through the systemic arterial circulation. Diffusion in the gas phase (within the alveoli) is inversely proportional to the square root of the molecular weight of a gas molecule. Diffusion into the liquid phase (pulmonary capillary blood) is directly proportional to the solubility of a gas molecule. Considering the respective molecular weights and solubility, CO_2 is about 20 times more diffusible than O_2. In health, the diffusion for both O_2 and CO_2 is complete by the time pulmonary capillary blood is no longer in contact with the alveolar gas. Clinically significant diffusion barrier manifests as hypoxia without impairing CO_2 elimination. Increasing FiO_2 and increasing alveolar-capillary O_2 gradient will improve oxygenation to some extent. However, even 100% O_2 is only about 5 times more concentrated than room air (as far as O_2 is concerned) while CO_2 is 20 times more diffusible than O_2. In other words, before hypercarbia to develop solely because of a diffusion gradient, life will be incompatible in presence of severe hypoxemia even while breathing 100% oxygen. Presence of hypercarbia suggests additional factors such as alveolar hypoventilation and ventilation/perfusion mismatch. Alveolar-arterial oxygen ($A\text{-}aO_2$) gradient is often utilized to monitor for oxygenation defects in impairment of diffusion and V/Q mismatch.

3.3 Distribution of Ventilation

Alveoli are perfused with systemic venous (pulmonary arterial) blood which gets arterialized after diffusion is complete. Pulmonary venous (systemic arterial) blood should have the same PO_2 and PCO_2 as in the alveolar gas. However, the arterial blood gas composition is different from alveolar gases even in normal individuals because alveolar ventilation (V) and perfusion (Q) are not matched uniformly. Some alveoli receive more ventilation compared to perfusion (high V/Q ratio, dead space ventilation units) while some receive perfusion in excess of ventilation (low V/Q ratio, shunt perfusion units). Ventilation perfusion (V/Q) relationships in a normal lung are easily understood by consideration of West Zones (Fig. 3.5)

Because of the lung recoil and gravitational force, the intrapleural pressure is more negative in non-dependent parts (upper lobes in upright position) of the lung compared to the dependent parts (lower lobes in upright position). At FRC, the alveoli in non-dependent areas of the lung are therefore at a more horizontal part of the pressure volume curve (more distended or aerated but less compliant) whereas the alveoli in the dependent areas are at a more vertical portion of the lung (less distended or aerated but more compliant). For the same change in intrapleural

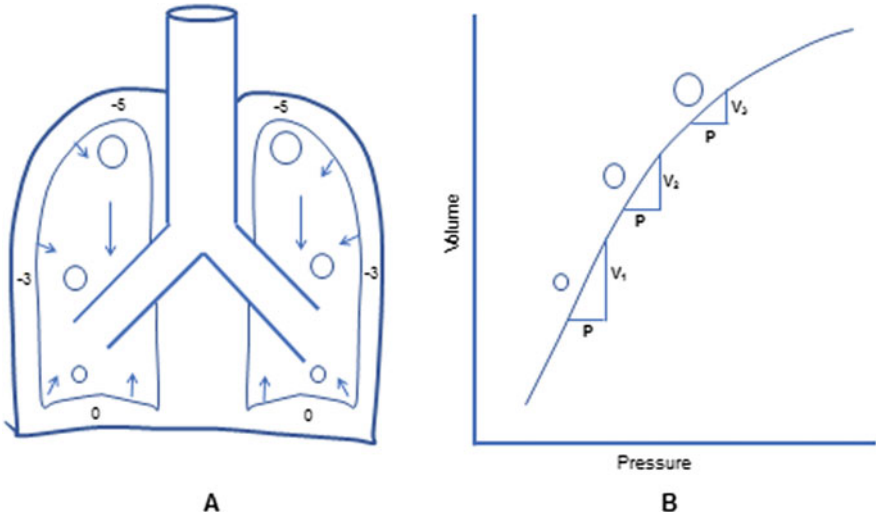

Fig. 3.3 **a** Illustrative representation of intrapleural pressures at FRC. Because of the lung recoil pressure and gravitational force, the intrapleural pressure is more negative in the non-dependent (upper lobes in upright position) portions of the lung compared to the dependent (lower lobes in upright position) portions. **b** Alveoli subjected to greater intrapleural pressure are therefore more distended (aerated) but less compliant. Alveoli that are surrounded by less negative pressure are less aerated but more compliant. For an identical change in inflation pressure, the change in volume is greater in dependent regions of the lung compared to non-dependent regions

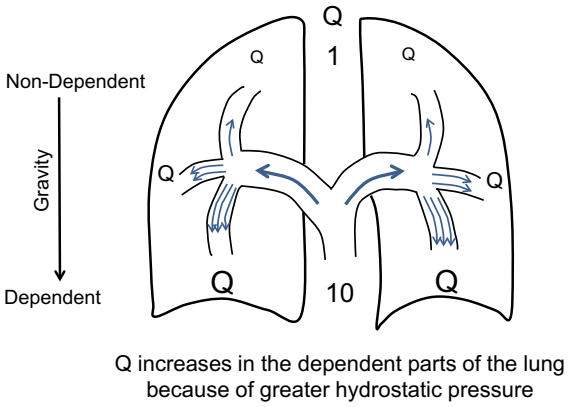

Fig. 3.4 Distribution of pulmonary perfusion is gravity dependent with dependent areas of the lung getting a larger share of the blood flow

pressure during inspiration, the dependent alveoli will receive greater portion of ventilation. At FRC, ventilation increases from non-dependent to dependent areas of the lung (Fig. 3.3).

3.4 Distribution of Perfusion

The distribution of perfusion is very much position dependent. In an upright individual, perfusion is greatest in the lower lobes (Fig. 3.4). In a supine position in which most critically ill patients are cared for, greater proportion of perfusion as well as ventilation are distributed to posterior regions of the lung.

3.5 Distribution of Ventilation and Perfusion

Because of the higher hydrostatic force aided by gravity, perfusion also increases from non-dependent portions to dependent portions. However, the increase in perfusion is considerably greater than the increase in ventilation. V/Q ratios favor ventilation in the non-dependent areas and they favor perfusion in the dependent areas. Although both ventilation and perfusion increase from dependent to non-dependent areas of the lung, the increase in perfusion is considerably greater than the increase in ventilation. While ventilation increases a little over 3 folds, the increase in perfusion may be as much as tenfold. The V:Q ratio is about 3:1 in the non-dependent and about 0.6:1 in the dependent parts of the lung. Thus, the V/Q ratios favor dead space ventilation in non-dependent parts and venous admixture in the dependent parts (Fig. 3.5). In situations such as ARDS, the dependent areas are more affected with capillary leakage. These areas receive less ventilation while still receiving larger share of perfusion. This leads to marked V:Q mismatch and

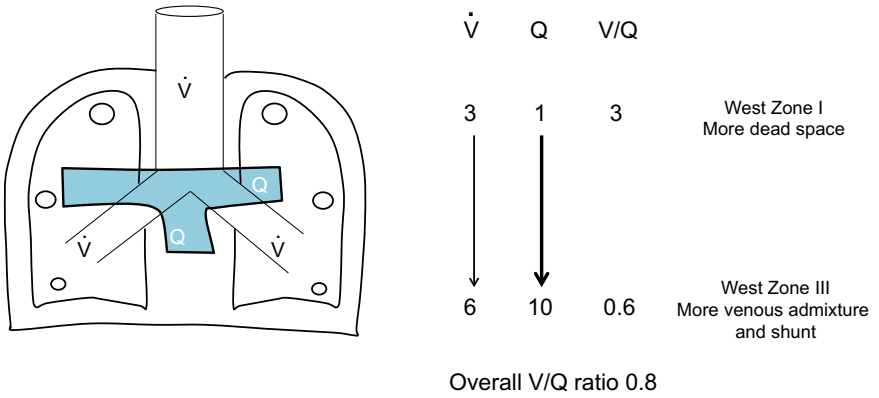

Fig. 3.5 Regional ventilation, perfusion and V/Q Ratios: Both ventilation and perfusion increase from non-dependent to dependent parts of the lung. The increase in perfusion is disproportionately greater than increase in ventilation resulting in V:Q ratios approximately 3:1 in non-dependent areas and 0.6:1 in dependent areas

hypoxemia. Caring such patients in prone position, shifts the perfusion to anterior portions of the lung which are less affected and better ventilated.

3.6 Regional V:Q Relationships (West Zones)

Alveolar pressure (P_A) , pulmonary capillary arterial pressure (Pa) and pulmonary capillary venous pressure (P_V) determine the type of V:Q relationship and they form the basis of West zones described by John West. In West zone I, P_A is > Pa which is > Pv. The alveolar pressure tamponades the pulmonary blood flow in Zone I. Ventilation is in excess of what is required to fully arterialize the pulmonary arterial blood amounting to wasted or dead space ventilation. Zone I is accentuated in hypovolemia, low cardiac output, pulmonary hypertension, excessive PEEP and pulmonary embolism. The overall VD/VT ratio is increased in Zone I. In West zone II, Pa is > P_A which is > P_V. Ventilation and perfusion are better matched in the sense the pulmonary arterial blood is adequately arterialized with appropriate amount of ventilation. In West zone III, both Pa and Pv exceed P_A resulting in a relationship of Pa > Pv > P_A. In these areas ventilation is insufficient to fully arterialize the pulmonary arterial blood thereby leading to venous admixture or right to left shunting. Zone III is increased in pulmonary edema, fluid overload and atelectasis. When using prone positioning in ARDS, the clinician attempts to improve V:Q matching by converting Zone III to Zone II type of V:Q relationship (Fig. 3.6).

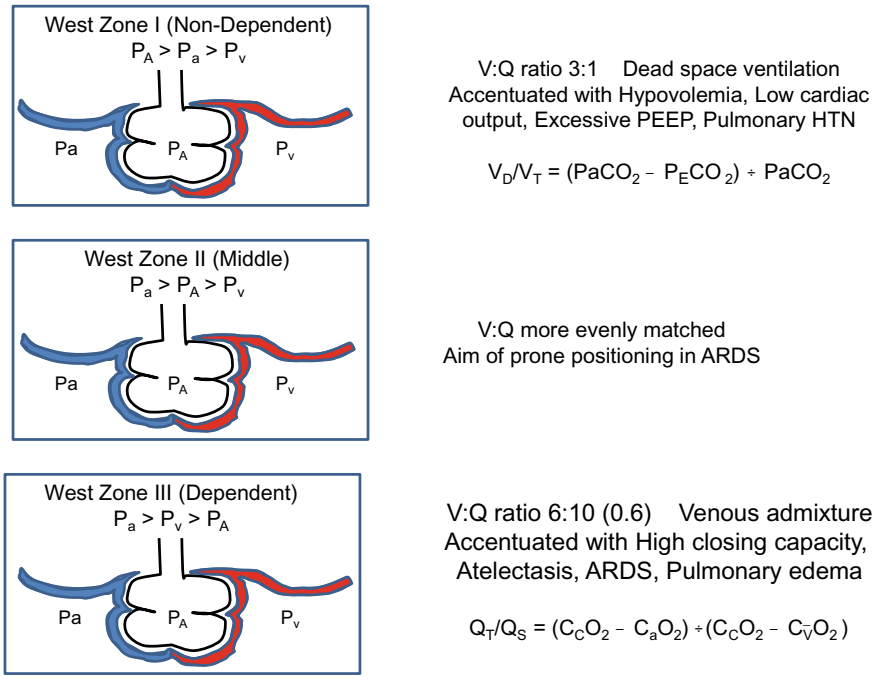

Fig. 3.6 Ventilation–Perfusion Relationship (West zones). Zone I is characterized by high V:Q ratios whereas Zone III has lower V:Q ratios

3.7 Ventilation (V) and Perfusion (Q) Mismatch

There are 3 prototypical V:Q relationships (Fig. 3.7). The first one is when ventilation is inadequate to fully arterialize the blood flowing past the hypoventilating alveolus. The end-result is a part (or all) of pulmonary capillary blood to remain variably deoxygenated and mix with the arterialized blood from other adequately ventilating lung segments. In this situation the arterial PO_2 (PaO_2) will be less than alveolar PO_2 (P_AO_2) as calculated by the alveolar air equation. The blood gas abnormality is referred to as venous admixture or intrapulmonary right to left shunt. The second V:Q relationship is when ventilation is appropriate for the given perfusion. In this situation, the pulmonary capillary blood is fully arterialized and PaO_2 and P_AO_2 are equal. The third V:Q relationship characterizes areas with decreased perfusion compared to ventilation. The part of the atmospheric air enters and leaves alveoli without contributing to the gas exchange. This type of V/Q mismatch is termed dead-space ventilation. In such situations P_ACO_2 is markedly less than $PaCO_2$.

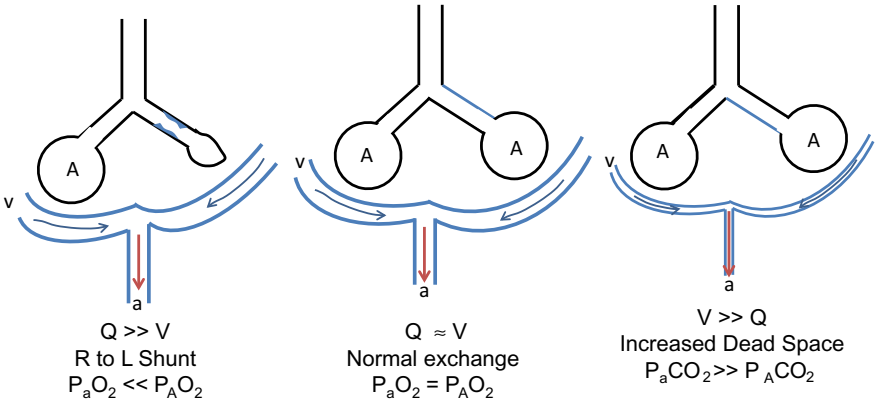

Fig. 3.7 Three types of V:Q relationship may exists: Normal V/Q, Shunt units and Dead space units

3.8 O_2 Transport and Utilization

The amount of oxygen carried by the arterial blood is in two forms: (i) in a dissolved state and (ii) combined with hemoglobin. The amount of dissolved oxygen is linearly related to PO_2. For every 100 torr PO_2, there is 0.3 mL oxygen dissolved in 100 mL of solvent. Dissolved O_2 serves two important functions. In this form O_2 is immediately available for tissue uptake. Dissolved oxygen also determines the extent to which hemoglobin is saturated by O_2. However this amount in and of itself, is hardly sufficient to satisfy tissue O_2 demands (Fig. 3.8).

The O_2 consumption for a healthy adult is approximately 250 mL/min. At a normal PaO_2 of 100 torr, there is 3 mL/L of dissolved O_2 in blood. If all of O_2 in blood was in the state of dissolved oxygen, it would require 83 L/min of cardiac output even if all of it were to be utilized by the body. The way hemoglobin associates and dissociates with O_2 constitutes an efficient means of transporting and utilizing oxygen. Each gram of hemoglobin when 100% saturated with O_2, carries 1.34 ml of oxygen. Thus, 15 G of hemoglobin per 100 mL of blood can carry approximately 20 ml of O_2 when nearly fully saturated with oxygen. This amounts to 200 mL of O_2 in 1000 mL of blood. With cardiac output of 5L per minute, an adult delivers 200 X 5 or 1000 mL of oxygen to the tissues every minute. With a resting O_2 consumption of 250 mL/min, as much as 750 mL (75% HbO_2 saturation) can still be returned back to the heart in mixed venous blood. Normally, arterial blood HbO_2 saturation is nearly complete much before we attain a normal PaO_2 because of the dissociation curve. For example, at PO_2 of 100 torr; hemoglobin-oxygen saturation is 97.5%, an increase of only 3.5% compared to the saturation at PO_2 of 70 torr where it is 94%. Relatively little O_2 can be added at higher PO_2s (Fig. 3.9).

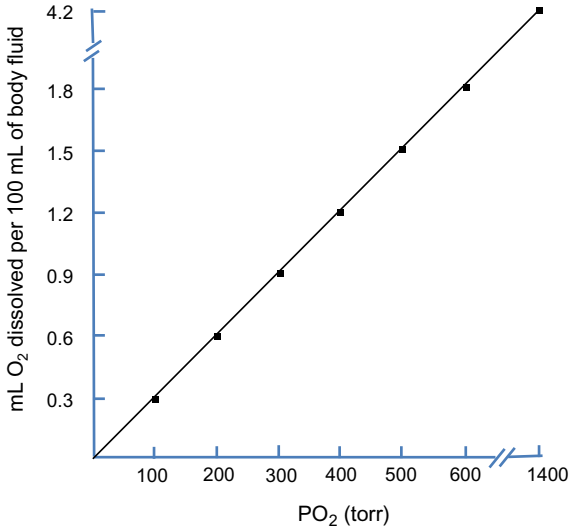

Fig. 3.8 Relationship of dissolved O_2 and PO_2 is linear. For every 100 torr, 0.3 ml of O_2 is in a dissolved state in a solution. Dissolved O_2 = (PO_2 in torr × 0.003)/mL of body fluid

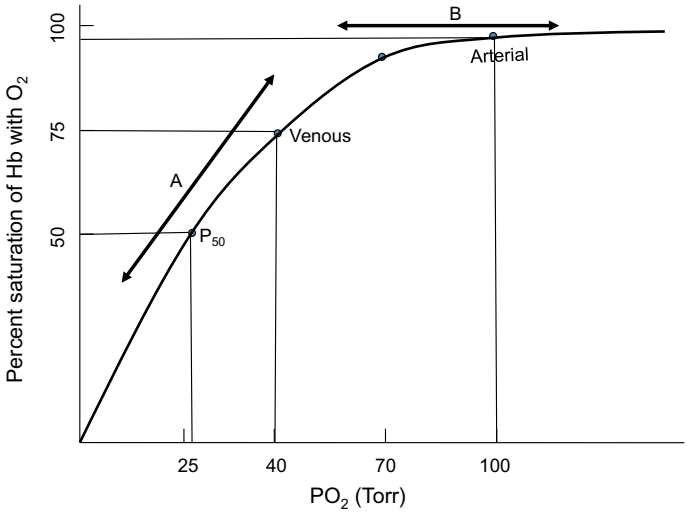

Fig. 3.9 Relationship of Hb-O_2 saturation and PO_2. In part of the curve labeled A, the change in the amount of Hb-O_2 saturation is considerably greater for a given change in PO_2 compared to the part labeled B. P_{50} refers to PO_2 at which Hb is 50% saturated

The hemoglobin molecule contains 4 heme chains each with an iron molecule in a reduced, ferrous (Fe++) state, and 4 globin chains. The spatial arrangement of the heme chains, Fe++ and globin chains is necessary for O_2 to bind reversibly with the heme part of the hemoglobin molecule. If the iron molecule is in an oxidized to a ferric state (Fe+ ++), methemoglobin is formed which is incapable of binding with O_2. Carbon monoxide (CO) reversibly binds with hemoglobin at the same sites as O_2 but with about 210 time greater affinity. Thus presence of mere 0.1% atmospheric CO will result in 50% carboxyhemoglobin (COHb) and 50% HbO_2 in arterial blood when breathing room air (21% O_2)! Both methemoglobinemia and CO poisoning can lead to life-threatening decline in blood O_2 content despite adequate PaO_2. 2,3-DPG, a product of RBC anaerobic glycolysis, plays an important part in association and dissociation of hemoglobin and oxygen. It binds with deoxyhemoglobin much more efficiently than with oxyhemoglobin. At lower PO_2 levels such as would occur in the tissues, 2,3-DPG facilitates O_2 to dissociate from the hemoglobin and make itself available for aerobic metabolism. At higher PO_2 levels such as would occur in the lung, oxygen binds more readily with hemoglobin not allowing 2,3-DPG to bind with hemoglobin. At high altitudes and in patients with anemia and other hypoxic conditions, 2,3-DPG concentration is increased allowing for greater release of O_2 to the tissues. Fetal hemoglobin has less affinity to 2,3-DPG and therefore it binds to O_2 more readily.

Several factors influence the shape of HbO_2 dissociation curve. A shift to the left or a decrease in P_{50} (PO_2 at which HbO_2 saturation is 50%) is a characteristic of fetal hemoglobin, hypothermia, alkalosis and a decrease in 2,3-DPG. On the other hand, a shift to the right or an increase in P_{50} is observed in hyperthermia, acidosis and an increase in 2,3-DPG. A shift to the right facilitates release of O_2 at the tissue level. (Fig. 3.10).

Following equations represent the relationship of arterial O_2 content (CaO_2), venous O_2 content (CvO_2), Cardiac output (CO), Oxygen delivery (DO_2), and Oxygen consumption (VO_2).

$$CaO_2 = [(Hb \times 1.34 \times SaO_2\%) + (PaO_2 \times 0.003)] \times 10$$

where CaO_2 is Oxygen content of blood in mL/L, Hb is Hemoglobin concentration in G/dL, SaO_2 is the Arterial Oxygen Saturation, PaO_2 is the Arterial Oxygen Tension in mmHg. Please note that the multiplication by 10 is to convert O_2 content/100 mL to O_2 content/1000 mL or 1 L.

Similarly, the oxygen content of mixed venous blood can be calculated as follows:

$$CvO_2 = [(Hgb \times 1.34 \times SvO_2\%) + (PvO_2 \times 0.003)] \times 10$$

Delivery of oxygen to the tissues by the circulatory system is estimated using the formula:

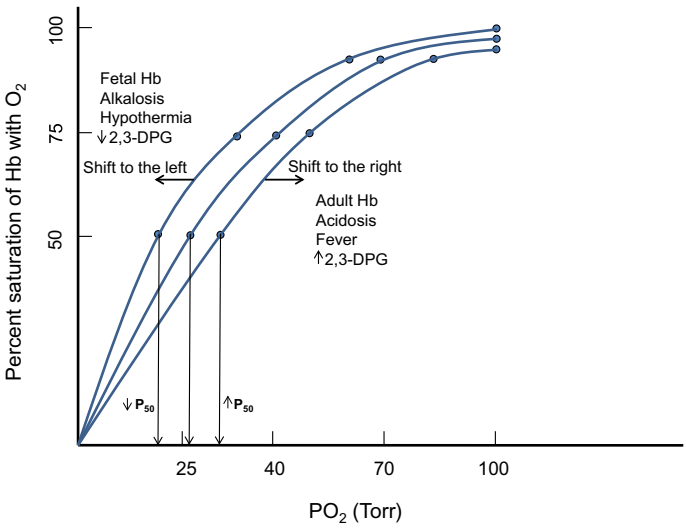

Fig. 3.10 HbO_2 dissociation curves shift to the left (increased O_2 affinity) or to the right (decreased O_2 affinity) under certain clinically encountered situations

$$\dot{D}O_2 = CaO_2 \times C.O.$$

where DO_2 is the delivery of oxygen in mL/min, CaO_2 is the arterial oxygen content in mL/L, and C.O. is the cardiac output in L/min.

Oxygen consumption by the tissues is measured in mL of oxygen per minute and is expressed as:

$$\dot{V}O_2 = (CaO_2 - C\bar{v}O_2) \times C.O.$$

where VO_2 is oxygen consumption per minute, CaO_2 is the arterial oxygen content, CvO_2 is the mixed venous oxygen content, and C.O. is the cardiac output.

The ratio of oxygen consumption to oxygen deliver is called Oxygen Extraction. It is the fraction of the oxygen delivery that is consumed by the tissues. It is calculated as follows:

$$Oxygen\,Extraction(O_{2Extr}) = \frac{\dot{V}O_2}{\dot{D}O_2}$$

Since Cardiac Output is in both the numerator and the denominator, oxygen extraction can be simplified as follows (Fig. 3.11):

$$Oxygen\,Extraction(O_{2Extr}) = \frac{(CaO_2 - C\bar{v}O_2)}{CaO_2}$$

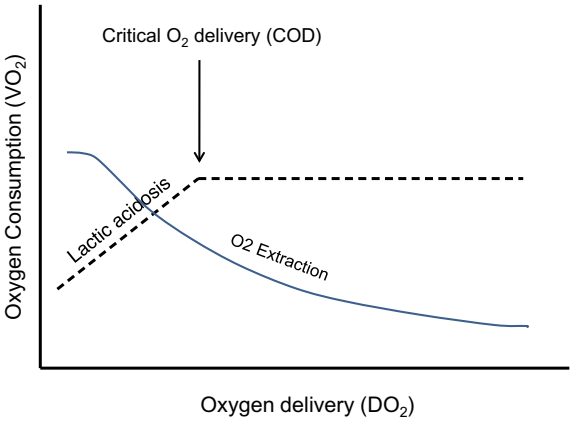

Fig. 3.11 As DO_2 decreases, VO_2 remains constant over a wide range by increasing O_2 extraction to maintain aerobic metabolism. Fall in DO_2 beyond a certain point (critical O_2 delivery) results in anerobic metabolism and lactic acidosis despite continued increase in O_2 extraction

Normal resting adult has DO_2 of approximately 1 L/min and VO_2 of 250 mL/min. Thus 75% of delivered O_2 is returned back to heart in the mixed venous blood. CvO_2 is a reflection of the DO_2-VO_2 relationship. For sake of convenience, SvO_2 is substituted for CvO_2 since most of the oxygen content is accounted for by hemoglobin saturated with O_2. The relationship between VO_2, DO_2 and O_2 extraction is shown in Fig. 3.11. When DO_2 is decreased, VO_2 is initially kept constant to maintain aerobic metabolism by increasing O_2 extraction. A decrease in DO_2 below a certain level results in a decreased VO_2 despite increased O_2 extraction. DO_2 below which increased O_2 extraction does not satisfy aerobic metabolic demand of the tissues is termed critical O_2 delivery (COD). When DO_2 falls below COD, anaerobic metabolism begins with accumulation of lactic acid. Provided VO_2 and CaO_2 remain unchanged, SvO_2 is an indication of adequacy of CO to maintain aerobic metabolism. Declining SVO_2 is suggestive of decreasing cardiac output.

3.9 Abnormalities of Gas Exchange

As outlined in the preceding discussion, several factors determine gas exchange at the alveolar capillary junction. Analysis of arterial blood gases provides both diagnostic clues as well as therapeutic approach in management of respiratory disorders. The challenge to the clinician is that arterial sample is often not available and a capillary blood sample has to be relied on in many circumstances. Also, a precise FiO_2 is usually not available in many patients. The clinician has to rely on many assumptions and clinical experience.

There are four main types of abnormalities in gas exchange. These are (a) alveolar hypoventilation (b) ventilation-perfusion (V-Q) mismatch (c) diffusion defects and (d) absolute right to left shunt (Table 3.2). In many patients more than one disorder may be present. For example, a patient with alveolar hypoventilation may also have a component of V-Q mismatch and a patient with a diffusion defect

may become exhausted and develop hypoventilation. In such a situation, the clinician must determine the major component of gas exchange abnormality to plan a targeted intervention.

Alveolar hypoventilation results when sufficient air is not moved in and out of the alveoli. There are 3 major types of clinical situations which manifest as alveolar hypoventilation. These are: airway obstruction above the carina (choanal atresia,

Table.3.2 Interpretation of arterial blood gas (ABG) values

Lesion	Effect	Typical ABG
* Central (above the carina) airway obstruction * Depressed respiratory center * Ineffective neuromuscular function	Uniform alveolar hypoventilation	* Early increase in $PaCO_2$ * Proportionate decrease in PO_2 depending on alveolar air equation * Response to supplemental oxygen: Excellent
Intrapulmonary airway obstruction	Venous admixture V/Q mismatch	* Mild: ↓ PCO_2, ↓ PO_2 * Moderate: "Normal PCO_2 ↓↓PO_2 * Severe: ↑ ↑PCO_2 ↓↓↓ PO_2 * Response to supplemental oxygen: Good
Alveolar-Interstitial pathology	V/Q mismatch, venous admixture, R to L shunt Diffusion defect	* Early decrease in PO_2 depending on severity * Normal or low PCO_2 * ↑ PCO_2 if fatigue occurs * Response to supplemental oxygen: Fair to poor
Extrapulmonary right to left shunt	Systemic venous blood bypasses alveoli, absolute R to L shunt	* Hypoxemia depending on magnitude of the shunt * Response to supplemental oxygen: Very poor

subglottic stenosis, vascular ring etc.), weakness of muscles of respiration (Guillain-Barré syndrome, myasthenia gravis, diaphragmatic paralysis etc.) and depressed respiratory center (CNS depressants, congenital central hypoventilation syndrome, brain stem dysfunction etc.). Airway obstruction below the carina may also manifest with predominant alveolar ventilation if the obstruction is relatively uniform such as in bronchiolitis obliterans. Alveolar ventilation is inversely proportional to $PaCO_2$; a certain percentage decline in alveolar ventilation [(Vt – Vd) x rate] will lead to an increase in $PaCO_2$ by a similar percentage. The hallmark of alveolar hypoventilation is elevated $PaCO_2$ and a proportionate decline in PAO_2 as determined by alveolar air equation;

For $FiO_2 < 1$, the equation can be simplified to:

$$PAO_2 = PiO_2 - \frac{PACO_2}{R}$$

For bedside calculations, $PACO_2$ is substituted for $PaCO_2$. Thus for a given PiO_2, PAO_2 will fall only by the rise in $PaCO_2 \div R$. Since R is assumed to be 0.8, the fall in PAO_2 will be approximately by rise in $PaCO_2 \times 1.25$. In the absence of significant parenchymal disease and intrapulmonary shunting, administration of supplemental O_2 will increase PiO_2 and readily reverse hypoxemia despite persistent hypercarbia.

In intrapulmonary airway obstruction (asthma, bronchiolitis, aspiration), the obstruction is not uniform in nature. Some areas are more obstructed than others while some still are relatively unaffected resulting in multiple areas having different extent of ventilation; some are hypoventilated while others are hyperventilated. Pulmonary capillary blood coming from hypoventilated areas has higher $PaCO_2$ and a lower PaO_2, whereas that coming from hyperventilated areas has lower $PaCO_2$ and higher PaO_2. A lower $PaCO_2$ can compensate for the higher $PaCO_2$ because the Hb-CO_2 dissociation curve is relatively linear. An equal amount of blood with $PaCO_2$ of 30 torr mixing with $PaCO_2$ of 50 torr will result in a $PaCO_2$ of 40 torr. A higher PaO_2 however cannot compensate for a lower PaO_2 in the presence of desaturated hemoglobin because of the shape of the HBO_2 dissociation curve. It is the % HbO_2 saturation that averages out since far more O_2 is responsible for combing with Hb than the dissolved O_2 reflecting the PO_2. For example, an equal amount of blood with PaO_2 of 25 torr and HBO_2 saturation of 50% mixing with PaO_2 of 110 torr and HbO_2 saturation of near 100% will result in HbO_2 saturation of 75% and PaO_2 of 40 torr. The blood gas abnormality in such situations is referred to as V-Q mismatch, venous admixture or partial right to left intrapulmonary shunting. In mild disease, the hyperventilated areas predominate outnumbering the hypoventilated ones. The end result is hypocarbia and respiratory alkalosis. An elevated PaO_2 in the hyperventilated areas however cannot compensate for the low PaO_2 in hyperventilated area resulting in mild hypoxemia. With increasing severity, more areas become hypoventilated resulting in normalization of $PaCO_2$ (crossover point) with a further progressive decline in PaO_2. A normal or slightly elevated $PaCO_2$ in intrapulmonary airway obstruction raises concern for

impending respiratory failure. As the disease severity increases, more and more lung units are hypoventilated, resulting in hypercarbia, respiratory acidosis and hypoxemia. Supplemental O_2 is effective if it is able to reach the hypoventilated alveoli.

In alveolar and interstitial pathology (ARDS, interstitial pneumonia, pulmonary edema), arterial blood gas values reflect intrapulmonary right to left shunting and diffusion barrier. Systemic venous blood flows across unventilated alveoli without getting oxygenated. The diffusion impediment is 20 times greater for O_2 than for CO_2. Hypoxemia developing early and getting progressively severe is a hall mark of such diseases. Most patients develop hyperventilation manifesting hypocarbia. An increase in $PaCO_2$ is observed only after muscle fatigue and exhaustion ensue. Response to supplemental O_2, while life-saving, may not be as robust as in other respiratory pathophysiologic alterations. In severe situations, hypoxemia may become resistant to O_2 therapy.

In conditions where systemic venous blood completely bypasses the alveolar-capillary bed (cyanotic heart disease, pulmonary arteriovenous fistula etc.), hypoxemia is the predominant feature as a fixed amount of deoxygenated blood mixes with oxygenated blood. Supplemental oxygen does not increase PaO_2 since the deoxygenated shunted blood has no chance of getting in contact with alveolar gas.

3.10 Regulation of Respiration

Blood gas homeostasis to suit the body's requirements is maintained by a complex interaction of controllers, sensors and effectors (Fig. 3.12). The central respiratory controller is represented by a group of neurons in the CNS that receives information from sensors and sends motor impulses to muscles of respiration which serve the function of the effectors. The most important effector is the diaphragm which is aided by the intercostal, abdominal and neck muscles as accessories when needed. The effectors target the lungs to adjust alveolar ventilation and control pH, $PaCO_2$ and PaO_2. The entire respiratory regulatory mechanism undergoes maturational changes from the neonatal to adult life. It is also subject to modifications by the sleep states, disease processes, pharmacologic agents and acclimatization to the environment.

3.10.1 Central Respiratory Controller

Two functionally and anatomically distinct group of neurons located in the CNS control the process of respiration: voluntary and automatic.

Voluntary control of respiration resides in the cerebral cortex and limbic forebrain areas. Major sensory inputs consist of smell, vision, emotions, pain, touch

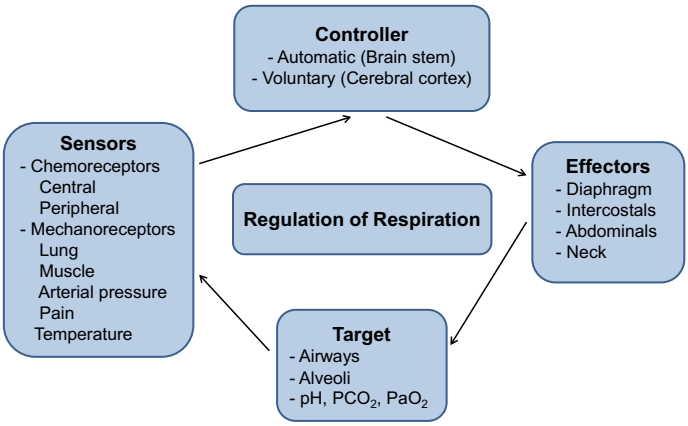

Fig. 3.12 Control of respiration

etc., and motor impulses are sent to the effectors through corticobulbar and corticospinal tracts. Voluntary control of respiration requires a certain level of consciousness, and is important for protection against aspiration and inhalation of noxious gases. Patient with toxic/metabolic/infectious/traumatic encephalopathies and pharmacologic sedation may lose voluntary control of respiration depending on the extent of CNS dysfunction.

Automatic control of respiration is located in the brainstem. Neuronal circuits, referred to as central pattern generators (CPGs) spontaneously generate rhythmic motor output without requiring conscious input, and are responsible for breathing, swallowing and chewing. CPGs responsible for breathing are located in pons and medulla. A group of neurons located in lower pons constitutes the apneustic center which is responsible for pronged inspiratory effort interrupted by brief periods of expiratory activity. Another group of neurons in the upper pons termed pneumotaxic center, is involved in inhibiting the activity of CPGs. The role of apneustic and pneumotaxic centers is to fine-tune the rhythmic respiratory activity of CPGs. Global CNS depression from any cause can manifest as slow and shallow respirations, hypoventilation and respiratory acidosis. Similarly, localized CNS lesions are manifested by specific patterns of abnormal ventilation.

3.10.2 Sensors

Multiple mechanisms exist that can sense abnormalities of gas exchange, acid–base imbalance and respiratory system dysfunction, and send that information to the central respiratory controller to modify the breathing pattern. These mechanisms exist in the form of sensory nerve endings termed chemoreceptors and mechanoreceptors depending on the type of stimulus that is being sensed.

Chemoreceptors are further classified as central or peripheral depending on their location.

Central chemoreceptors are located within the CNS. They reside over a wide area that includes posterior hypothalamus, cerebellum, locus ceruleus, raphe and brain stem. They sense a change in chemical composition of the body fluid they are exposed to. Central chemoreceptors respond to the chemical changes in the extracellular fluid (ECF) of the brain represented by cerebrospinal fluid (CSF). The ventilatory response is predominantly due to a change in the H^+ concentration (pH) of the brain ECF. The brain ECF and blood are separated by the blood brain barrier which is relatively impermeable to H^+ and HCO_3^- but freely permeable to PCO_2. A rise in $PaCO_2$ is quickly reflected in a rapid rise in the CSF PCO_2. The consequent fall in CSF pH is sensed by the central chemoreceptors which then send excitatory impulses to the controller resulting in increased ventilation via the effectors. CSF pH in normal conditions is slightly acidic, around 7.32. With its lower protein level and absence of hemoglobin, CSF also has much less buffering capacity compared to that of the blood. Consequently, for an equivalent change in $PaCO_2$, the change in CSF pH is much more pronounced than that in the blood. In disease states characterized by chronically elevated $PaCO_2$, the CSF pH tends to normalize as HCO_3^-eventually equilibrates across the BBB. Patients with chronically elevated $PaCO_2$ therefore have a relatively normal CSF pH and they do not have the same ventilatory response that is observed with acute hypercarbia.

Peripheral chemoreceptors are clusters of cells referred to as carotid bodies just above the bifurcation of the common carotid and external carotid arteries, and aortic bodies above and below the aortic arch. Carotid bodies are far more powerful sensors than aortic bodies. The cells comprising carotid and aortic bodies have a very high metabolic rate as well as blood flow to meet their metabolic demands. The main stimulus for peripheral chemoreceptors is hypoxia. Decrease in PaO_2 (SaO_2), blood flow (low cardiac output), and impaired O_2 utilization (cyanide poisoning) classically described as hypoxemic hypoxia, stagnant hypoxia and histotoxic hypoxia respectively, are potent stimulators of peripheral chemoreceptors. Anemia and dyshemoglobinemias do not stimulate peripheral chemoreceptors as long as PaO_2 and cardiac output are adequate. This is because the dissolved oxygen in the blood in form of PaO_2 and high blood flow easily satisfy the exceptionally high O_2 requirement of the chemoreceptors. Relationship of PaO_2 and stimulation of peripheral chemoreceptors is non-linear. Chemoreceptor stimulation begins at PaO_2 below 500 torr and a small increase in ventilation occurs incrementally until PaO_2 reaches 100 torr. The response time for peripheral chemoreceptor is much faster than central chemoreceptor stimulation. Even during normal respiration, carotid bodies response rate is fast enough to alter their discharges sensing small cyclic changes in PaO_2 during inspiration and exhalation. At PaO_2 less than $\sim$ 50 torr, carotid body stimulation increases exponentially. Subjective feeling of dyspnea from pure hypoxia alone does not occur until PaO_2 falls below $\sim$50 torr (SaO_2 below $\sim$ 85%). Peripheral chemoreceptors account for almost all the hyperventilation response to hypoxia. They also respond to PCO_2 but the increase in alveolar ventilation per torr PCO_2 is much less than that from central