Textbook of PULMONARY AND CRITICAL CARE MEDICINE

Second Edition

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Foreword

The 2nd edition of this *Textbook of Pulmonary and Critical Care Medicine* edited by SK Jindal, Professor Emeritus, Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India, again offers a thoroughly comprehensive and practical reference for the clinicians, who care for patients with respiratory diseases and critical illnesses. It is a timely follow-up to the 1st edition, given the rapid developments and advances in these fields. While this textbook will have special appeal and value to the physicians of the South-Asian continent, I can attest to the fact that it offers an authoritative addition to any practitioner’s library. After receiving my copy of the 1st edition, I found myself frequently turning to the book for a refresher on topics related to the patients under my care.

I also used this textbook to supplement my lectures and seminar materials for the medical students and physicians-in-training. This new edition provides educational value for the educators, pulmonologists, intensivists, thoracic surgeons, pediatricians, postgraduate trainees, and students of medicine. It is especially unique because of the abundance of illustrations, flow charts and tables. Their clarity and, at times, simplicity, make them valuable for the novice and also very useful for the educators. The large number of radiographic and pathologic reproductions are also great teaching tools.

Once again, in this field, Professor SK Jindal has enlisted the collaboration of his colleagues from the Postgraduate Institute of Medical Education and Research in Chandigarh and of leading experts at medical schools in India and in many other countries around the globe. As a result, the textbook offers a unique exposure to special problems seen in different parts of the world. One such problem is tuberculosis (TB). Despite the fact that nearly all the cases can be cured, the WHO considers TB one of the world’s biggest threats. Fifteen chapters in this book are devoted to the topics of TB, ranging from epidemiology and risk factors to the challenges in treating routine, multidrug resistant and surgically correctable disease. This section is a highlight of the book and, based on the recent WHO statistics, education about TB continues to be a high priority in highly endemic areas. For example, of the 9.6 million new cases of TB in 2014, 58% were in Southeast Asia and West Pacific Region, whereas India, Indonesia and China accounted for 23%, 10% and 10% respectively of the total globally, and more than half of the multidrug-resistant TB has occurred in India, China and the Russian Federation. The WHO report 2015 heralds an end-TB strategy to reduce TB deaths by 90% by the year 2030—a target, the readers of this book can help to achieve.

As in the previous edition of the book, there are chapters that are very helpful especially to the practicing physicians, including those who offer a systematic approach to clinical problems including, cough, dyspnea and hemoptysis, the interpretation of plain chest radiographs, the approach to chest CT scans, and the microbiologic approach to respiratory infections. An overview of the antimicrobial and immunosuppressive pharmacologic agents used to treat lung disease, is extremely useful.

What is most impressive about this edition of the book is that it continues to be comprehensive, practical, and updated. There is hardly any topic missing that might be within the scope of this book. The physicians and clinicians around the globe will benefit from Professor SK Jindal’s extensive efforts.

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Preface to the Second Edition

The 1st edition of this *Textbook of Pulmonary and Critical Care Medicine* received huge success all over the world. This edition, in its two volumes with over 200 authors from over 12 different countries, will serve as a reference book for the students and teachers of medicine and pulmonary sciences. There has been a constant demand for the new edition from various sections for over a year. Therefore, last year, we took the decision to revise the 1st edition.

Tremendous changes have happened in the practice of medicine including those in pulmonary medicine. Rapid advances in technology, introduction of new drugs, devices and diagnostic investigations, have made it mandatory to provide updated information to our readers. Although we have tried our best to include references to the latest publications up to the year 2016, it has not been possible in all the cases because of the longer time period required to publish such a huge text.

Electronic publications and wider availability of information on the internet seems to have relegated the printed books to the background. But textbooks remain irreplaceable. One cannot opt for shortcuts in acquisition of information and knowledge of a subject especially during training or a degree program. Internet browsing tends to promote abbreviated information, which goes against the tenets of a comprehensive program. Undoubtedly, the internet and electronic books offer great help to provide supplementary as well as complementary information. A large majority of students as well as teachers, however, continue to pose greater confidence in the print version, especially in case of the ‘Text’ and ‘Reference’ books.

There has been an enormous increase in the global burden of ‘noncommunicable diseases’ recognized by the UN General Assembly in one of its ‘resolutions’, which has made it incumbent upon all the countries to take effective steps for the control and management of these diseases. Chronic pulmonary diseases constitute one major component of this burden. Factually, the ‘Third-world’ countries suffer from an increasing onslaught of both communicable and noncommunicable diseases. On the other hand, the developed countries too are not immune from infectious diseases. Respiratory system is the most favored target of infectious diseases as much as of noncommunicable diseases.

We have seen a rapid expansion of pulmonary and critical care services all over the world. In India, for example, there was only one postdoctoral fellowship (DM) ‘program in pulmonary and critical care medicine’ in 2011, when the 1st edition of this book was published; there are at least seven such programs now in India. This has resulted in a greater visibility of the specialty as well as an increased demand for the teaching-learning material. Parallelly, there are enormous advancements made in interventional pulmonology and pulmonary critical care as well as the emergence of subspecialties such as ‘sleep medicine, allergy-immunology, environmental and occupational medicine’. The increased concern about ambient and indoor air pollution as a cause of pulmonary diseases, has added an extra burden on pulmonary trainees. We have taken care to incorporate all the important areas of pulmonary medicine that might be within the scope of this book.

This current edition of the book has several new authors and topics in the text. On the other hand, some of the chapters of the earlier edition have been either pruned or deleted altogether. That has been done only to make it more interesting and reader-friendly.

SK Jindal
Preface to the First Edition

It was merely a quarter of a century ago when the specialty of pulmonary medicine was factually recognized as an important division of medicine. Until then, the lung diseases were generally dismissed as tuberculosis, or non-descriptive pneumonias and infections. Most of the nontuberculous lung diseases remained either undiagnosed or unknown. Of course, several stalwarts of the sixties and seventies had clearly identified this deficiency and made efforts to define the pulmonary problems and plan their solutions.

It was in 1989 that the first independent, postdoctoral DM Fellowship Program in Pulmonary Medicine was started at Chandigarh. Subsequently, the program was expanded to include the Critical Care as an essential component of the DM training. In addition, there were several postgraduate MD and/or diploma courses in tuberculosis and chest diseases, and/or respiratory diseases at different medical colleges. Unfortunately, most of the postgraduate programs lacked in their curricula especially for nontuberculous diseases and other systemic disorders. Moreover, the on-hand training in diagnostic and treatment modalities had been highly inadequate in the postgraduate courses. It is rather enigmatic that we still continue to lack the dedicated thoracic surgery courses and texts in various countries.

The increased importance and scope of respiratory and critical care medicine had also necessitated the need to develop the indigenous teaching and training materials including the texts with incorporation of local problems and possible solutions. Undeniably, the science is the same all over the world, but the experiences are different. Excellent text and reference materials on the subject have been available for long, which continue to guide the students, teachers and practicing physicians. In the present literature, quite a few textbooks of pulmonary medicine have been published. Ours is one more attempt in this direction to add to the existing literature on lung diseases available worldwide. This book contains contributions by approximately hundred international esteemed pulmonary medicine consultants and teachers.

There are, however, a few important additions in this present textbook. It is fairly comprehensive with contributions from several internationally eminent authors. It includes the basic principles as well as the recent advances related to different subjects. We have also attempted to incorporate allied clinical sciences relevant to the practice of the pulmonologists. A classical example is the critical care which forms an integral component of pulmonary medicine. It also incorporates tuberculosis, other pulmonary infections, environmental and occupational medicines, sleep disorders and general systemic diseases affecting the respiratory system in one or the other way. Although the critical care is relevant to most of the medical and surgical specialties, the pulmonologists have a more vested interest than that of the other specialists. Assisted respiration, which forms the core of most critical care, lies in the primary domain of pulmonologists.

We have taken care not to forget the need to push forward and meet the goals of excellence in health care. The real test of merit of a book lies in its readership by the students and adoption of its recommendations in clinical practice. Hopefully, the material in the text will benefit a diverse category of people including internists, general physicians, pulmonologists, pediatricians, intensivists, anesthesiologists and others, who need to handle patients with respiratory diseases and critical care.

SK Jindal
I thankfully acknowledge the contribution of my colleagues Dr D Behera, Dr Ashutosh N Aggarwal, Dr Ritesh Agarwal, Dr Navneet Singh, Dr Sahajal Dhooria and Dr Inderpaul Singh Sehgal, for their continued help in editing the manuscript. Unfortunately, we untimely lost our colleague Dr Dheeraj Gupta, while this edition of the textbook was still in its infancy. He had been a great source of encouragement and inspiration, the primary force in bringing out the 1st edition. Aditya, my son, has been only partially successful in bridging the gap.

I am immensely grateful to Dr Sidney S Braman, Dr Richard S Irwin, Dr Suhail Raoof, Dr PS Shankar, Dr Kalaplatha K Guntupally, Dr Ruby Pawankar and others, who have significantly contributed to this textbook. A large number of friends and eminent colleagues from across the globe have unhesitatingly spared their time as authors and coauthors with their valuable chapters and wisdom, for which, I remain obliged to them. I also greatly appreciate the help rendered by my erstwhile secretary, Ms Manju Aggarwal, for the preparation of the manuscript.

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INTRODUCTION

Oxygen is essential for continuation of life. It is required by each human cell for its survival. It is abundantly present in atmosphere and maintains a remarkably constant concentration of 20.9% in ambient air. Oxygen is taken up by lungs through the act of inspiration and transported to cells via blood. At the cellular level, oxygen is utilized for production of energy. In this process, carbon dioxide is released and transported back via blood to lungs from where it is expired out into atmosphere. The act of exchange of oxygen and carbon dioxide is called respiration. For effective respiration, air must be drawn through the airways and distributed among approximately 400,000,000 alveolar compartments within the lung parenchyma. Although respiration is normally described as uptake of oxygen and release of carbon dioxide by the lungs, it is essentially happening at the level of lungs (“external” respiration), as well as the tissues (“internal” respiration).

The respiratory system is made up of a gas exchanging organ (the lungs) and a pump that ventilates the lungs. The pump consists of the chest wall and the respiratory muscles, which increase and decrease the size of the thoracic cavity; the areas in the brain that control the muscles; and the tracts and nerves that connect the brain to the muscles. At rest, a normal human breathes 12–15 times a minute. About 500 mL of air per breath, or 6–8 L/min, is inspired and expired. This air mixes with the gas in the alveoli, and, by simple diffusion, O₂ enters the blood in the pulmonary capillaries while CO₂ enters the alveoli. In this manner, 250 mL of O₂ enters the body per minute and 200 mL of CO₂ is excreted.

Gas exchange by human lungs is achieved with the help of four processes (Fig. 1), which are also variably interdependent:

1. Ventilation: To and fro movement between the atmosphere and the gas exchanging units of lung.
2. Circulation: Supply and distribution of blood through the pulmonary capillaries.
3. Diffusion: The movement of O₂ and CO₂ across the air-blood barrier between alveoli and pulmonary capillaries.
4. Ventilation-perfusion relationships.

VENTILATION

Ventilation is the process of bulk movement of air from atmosphere, through the conducting airways to the terminal respiratory gas exchange units. This movement of air is made possible by force which is generated by effort of respiratory muscles (or a mechanical ventilator if the patient is being ventilated). It is also dependent on mechanical properties of the conducting airways and the lung parenchyma (i.e. the breathing units). The mechanical properties are referred to as “static” at zero (or no airflow) flow and constant volume, and “dynamic” if there is air flow.

The amount of air that moves in and out of the lungs with each inspiration and expiration respectively is called
the tidal volume. The air inspired over and above the tidal volume with a maximal inspiratory effort is the inspiratory reserve volume, and the volume exhaled actively after passive expiration is the expiratory reserve volume; the air left in the lungs after a maximal expiratory effort is the residual volume. The respiratory dead space is the space in the conducting zone of the airways occupied by gas that is not involved in gas exchange. The vital capacity, the largest amount of air that can be exhaled after a maximal inspiratory effort, is a frequently measured index of pulmonary function. The fraction of the vital capacity exhaled during the first-second of a forced expiration is the FEV$_1$. The maximal voluntary ventilation is the largest volume of gas that can be moved in to and out of the lungs in 1 minute by voluntary effort. There are several factors on which the aforementioned lung volume and the airflow depend: Compliance (a volume term), which is a measure of the elastic properties of lung, is an important determinant. Other elements include resistance (a flow term) and inertance (an acceleration term).

Inertance

Since the respired gases, the lungs and the chest wall all have appreciable mass and therefore inertia, they offer an impedance to change in the direction of gas flow. This component called inertance, is extremely difficult to measure, but offers impedance that increases with frequency. Hence, inertial pressure is essentially negligible for most clinical purposes and the gas flow depends primarily on the compliance and resistance characteristics of the lung parenchyma except in situations of increased respiratory frequencies like high-frequency ventilation.

Compliance

Pulmonary compliance (or distensibility) is defined as the change in the volume of lung per unit change in distending pressure, which in case of lung is the transpulmonary pressure [defined as the pressure gradient between the alveolar ($P_A$) and the pleural pressures ($P_{pl}$)]. Elastance is the reciprocal of compliance. Compliance is equal to exhaled tidal volume (or a change in lung volume) divided by alveolar pressure minus the pleural pressure (or a change in the transpulmonary pressure).

$$C = \Delta V_L / \Delta (P_A - P_{pl})$$

where $C =$ lung compliance, $\Delta V_L =$ change in lung volume, $\Delta (P_A - P_{pl}) =$ change in transpulmonary pressure.

The interaction between recoil of the lungs and recoil of the chest can be demonstrated using body plethysmography. The technique is described in detail in the chapter on pulmonary function testing.

The lung pressure volume relationship is a curvilinear graph. The elastic recoil pressure of lung always tends to collapse the lung even at the residual volume. Theoretically therefore, if removed from the thoracic cage, the lungs collapse to almost an airless state.

Hysteresis

The pressure-volume curve is also slightly greater when measured during deflation than when measured during inflation, a property called hysteresis (Fig. 2). Hysteresis is affected by the elasticity of lung parenchyma and the surface tension of alveolar spaces. In fact, hysteresis is a universal property of all elastic materials. Pulmonary compliance is normally measured in the pressure range where the relaxation pressure curve is steepest. However, compliance depends on lung volume with highest compliance at residual lung volume and low compliance at high lung volumes.

Recruitment

This is a unique phenomenon observed in lung due to closure of some small airways at lower lung volumes. As the transpulmonary pressure rises, the closed airways open sequentially. Thus, the recruitment of additional lung units in the initial phase of inspiration starting from lower lung volumes also contributes to hysteresis. Two other important factors affecting lung compliance are the surface tension and the physical nature of lung tissues.

Surface tension exerted by air fluid interface is reduced by surfactant—a surface active compound of phospholipids produced by type II alveolar cells. Surface tension is further
lowered at lower lung volumes thereby increasing the compliance and decreasing the force required during the next inflation. Also, by the Laplace law (Pressure = 2 × surface tension/radius), as the diameter of the alveoli is decreased, the pressure would increase and this would create an unstable system; this is also prevented by surfactant, which decreases surface tension with decreasing radii of alveoli, and allows gas to flow from the larger to the smaller alveolus and stability is maintained. This phenomenon is also mandatory for the maintenance of stability of alveoli at lower lung volumes.

Physical elastic properties of lung tissue per se, are due to the presence of elastic fibers in the pulmonary interstitium. Expansion in lungs is probably more due to unfolding and geometric rearrangement of elastic fibers rather than the actual lengthening. Aging alters the elastin and collagen fibers in lungs, thus increasing the compliance. Compliance is also increased in emphysema due to loss of elastic fibers of alveolar walls. It is reduced wherever there is stiffness and thickening of alveolar septae by processes such as fibrosis.

**Elastic Properties of Chest Wall and Lung-chest Wall Interactions**

The resting volume of thoracic cage is approximately equal to 70% of total lung capacity (TLC). It implies that if thoracic cage is opened and support of lung withdrawn, it expands from functional residual capacity (FRC) (the resting position of respiratory system at which the inward elastic recoil of the lungs is exactly balanced by the outward recoil of thoracic cage) to a volume of about 70% of TLC. At volumes less than 70% (including FRC), thoracic cage has a tendency to expand and elastic recoil pressure is opposite to that of lungs, and is directed outward.

The total compliance of the respiratory system is analogous to the electrical capacitance with the compliance of the lung and the thoracic wall arranged in series. Thus, the reciprocal of total compliance is the sum of reciprocals of the individual compliances, i.e.

\[
\frac{1}{\text{total compliance}} = \frac{1}{\text{lung compliance}} + \frac{1}{\text{chest wall compliance}}
\]

Instead of compliance, we may consider its reciprocal, elastance and the relationship is much simpler:

\[
\text{Total respiratory system elastance} = \text{lung elastance} + \text{chest wall elastance}.
\]

**Resistance**

Resistance is the opposition to motion and in the respiratory system opposition to the flow of gas. In the lung, resistance to air flow is of two types: tissue and airway. The former, also known as elastic resistance (resistance from tissues or tissue resistance), occurs when no gas is flowing, and is due to elastic resistance of lung tissue and chest wall and the resistance imparted from surface forces at the alveolar gas/liquid interface. Approximately, 80% of the pulmonary resistance is due to airway resistance or nonelastic resistance.

Resistance to airflow is computed by the simultaneous measurements of airflow, and the driving pressure that is required to achieve the flow, i.e.

\[
\text{Resistance} = \frac{\text{Driving pressure}}{\text{Flow}} = \frac{P}{V}
\]

Most nonelastic resistance is provided by frictional resistance to airflow and thoracic tissue deformation, with small contributions from inertia of gas and tissue and compression of intrathoracic gas.

**Airway Morphology**

Airways are tubular structures designed to carry air to alveolocapillary membrane for gas exchange. The tracheobronchial tree consists of several branches, which arise by dichotomous divisions of the parent bronchus. Airway divisions from trachea to the alveoli are not uniform, may vary between 10 and 25 in different areas—divisions being less near the hilar regions and more at the bases. The diameter, angulation and course of the bronchial divisions are also different in different lung zones. For example, the air passages to alveoli at the lung bases are straighter and have larger cross-sectional areas. This asymmetric pattern of branching is referred to as “irregular dichotomy”. It has a bearing on the distribution of ventilation and deposition of inhaled material.

Airways are classified into two types—conducting and respiratory airways. The conducting or central airways do not participate in gas exchange. They are larger than 2 mm in diameter, have cartilaginous support, are lined by ciliated columnar epithelium and are supplied by systemic bronchial circulation. They are also able to change their diameter in response to several neurohormonal and chemical stimuli due to the presence of smooth muscles in their walls and vagal innervation. The respiratory bronchioles or terminal airways are situated beyond the conducting airways. They are less than 2 mm in diameter, lack cartilaginous support, are lined by cuboidal epithelium and supplied by pulmonary circulation. Due to their structural properties, they are susceptible to compression and closure in response to changes in intrapulmonary pressures.

The geometric features of airway divisions have a direct relationship with the partitioning of resistance and hence distribution of ventilation. There is a progressive narrowing and shortening of airways as the division progresses from trachea to the peripheral airways. Despite reduction in the diameter of daughter airways, the total cross-sectional area increases tremendously as we go peripherally. This is because the total number of airways increases geometrically with each division and the diameter of each daughter airway is more than half of the parent airway. This results in almost 2,000 fold increase in total cross-sectional area from trachea to peripheral airways.
Physical Principle of Gas Flow and Resistance

The geometric features described above are important in the distribution of resistance within the lung. The air flow decreases progressively as air moves down the bronchial tree to the peripheral zones. In the terminal bronchioles, flow is reduced to almost zero. It is the Brownian motion of the molecules, which facilitates diffusion across the alveolocapillary membrane. As the flow velocity decreases, the driving pressure and resistance also fall. It has been calculated that 80% of total measurable resistance at mouth is contributed by central or conducting airways.

The precise relationship between pressure difference and flow rate depends on the nature of flow, which may be laminar, turbulent or a mixture of the two. With laminar flow, gas flows along a straight unbranched tube as a series of concentric cylinders that slide over one another, with the peripheral cylinder stationary and the central cylinder moving fastest, the advancing cone forming a parabola. The advancing cone front means that some gas will reach the end of the tube despite the volume of gas entering the tube being less than the volume of the tube. This has relevance in patients being ventilated using high frequency ventilation where there is significant alveolar ventilation despite the tidal volume being less than or equal to the anatomical dead space.

In a straight unbranched tube, the Hagen-Poiseuille equation allows gas flow to be quantified: Flow rate = ΔP × π × (radius)^4/8 × length × viscosity, where ΔP is the pressure gradient and equals the product of flow rate and resistance: Thus, resistance = 8 × length × viscosity/π × (radius)^4.

In this equation, the fourth power of the radius explains the critical importance of narrowing of air passages. With constant tube dimensions, viscosity is the only property of gas that is relevant under the conditions of laminar flow. Helium has a lower density, but a viscosity close to that of air, and thus will not improve gas flow if the flow is laminar.

On the other hand, turbulent flow occurs when gas flows at high rates through unbranched or irregular tubes, resulting in formation of eddy currents. In contrast to laminar flow, it has a square front and the volume of gas entering the tube is equal to the volume of the tube, the so-called bulk flow. The relationship is different from the laminar flow in that the driving pressure is proportional to the square of gas flow rate and the density of gas, but independent of its viscosity and the required driving pressure is inversely proportional to the fifth power of the radius of the tubing (Fanning’s equation).

The change in flow from laminar to turbulent characteristics is determined by a dimensionless number, the Reynolds’ number (N_Re), which is N_Re = density × velocity × diameter/viscosity. The property of gas that affects N_Re is the ratio of density to viscosity. Flow is laminar with N_Re less than 2,000, and changes from laminar to turbulent when the N_Re exceeds 4,000. Between N_Re of 2,000 and 4,000, both types of flow coexist. There is also a critical length of tubing before the parabolic pattern of laminar flow is established, and thus for gases with low N_Re not only will resistance be less during turbulent flow, but also laminar flow will become established more quickly after narrowed airways. In principle, turbulence occurs only in larger airways and not in smaller airways because of the large cross-sectional area, the small diameter and the slow velocity of the small airways. Heliox has a density/viscosity ratio of 0.31 compared to one for oxygen. It has a lower N_Re and higher potential for laminar flow, explaining its usefulness in patients with large airway diseases.

Total and Alveolar Ventilation

The total amount of air inhaled with each inspiration gets distributed in the lungs depending upon the regional resistance and compliance of different lung units. Ventilatory requirements for adequate supply of oxygen and removal of carbon dioxide depend on metabolic demands of body. The resting ventilatory requirements are small and are met with minimal expenditure of energy. A normal individual can maintain gas exchange with a ventilation of about 80 mL/kg/minute, which is about one-tenth of the maximum ventilatory capacity. Therefore, there is a vast reserve in ventilatory capacity and problems of gas exchange would not occur, if all the inspired volume is available to the gas exchange units. Due to cyclical nature of ventilation, a significant proportion of inspired gas never reaches the alveoli—a volume known as the dead space volume. So, the total ventilation is contributed by the dead space ventilation (V_D) and alveolar ventilation (V_A), i.e. the air that reaches the alveoli to take part in gas exchange. The dead space ventilation in mL is roughly around the individual’s body weight in pounds.

The volume of conducting airways, which constitute the anatomical dead space, is relatively fixed, i.e. about one-third of the resting tidal ventilation. Its relative proportion to the total ventilation decreases as the total ventilation increases, for example on exercise. On the other hand, a decrease in tidal volume and increase in respiratory rate (e.g. rapid shallow breathing) markedly increases the proportion of dead space ventilation thereby affecting gas exchange.

Dead space is also increased when there is presence of lung units, which are adequately perfused, but not ventilated, the so-called physiological dead space. It is important to distinguish between the anatomical dead space (respiratory system volume exclusive of alveoli) and the physiologic dead space (volume of gas in the alveoli not equilibrating with blood, i.e. wasted ventilation). As will be discussed subsequently in this chapter, ventilation has to be matched by the perfusion of blood in the alveolar capillaries for adequate gas exchange to occur. Ventilation and perfusion are not homogeneously distributed throughout the lung, and areas which receive more ventilation relative to perfusion result in wasted ventilation and thus add to “dead space” ventilation. The sum of the dead space ventilation by these two mechanisms constitutes “total dead space” and is given the formula:

\[ \frac{V_D}{V_{\text{es}}} = 1 - P_{\text{E}}CO_2/P_{\text{A}}CO_2 \]

where
DISTRIBUTION OF VENTILATION

Alveolar ventilation is distributed throughout the lungs. With each inspiration, around 500 mL of air is distributed to around 300 million alveoli such that each alveolus receives an appropriate share of the inspired gas. This fine distribution of air is essentially a function of the “time constants” of the regional lung units. Time constant is the product of regional compliance and resistance and thus is also called the RC time constant. The relative distribution of ventilation between two neighboring lung units can be understood better with the two compartment lung model. In health, the resistance and compliance of two adjacent units of lung are essentially equal and thus their RC time constant is normal with the normal distribution of ventilation. However in a diseased lung, different portions of lung may have abnormal time constants as a result of either the diseased airway lumen (increased resistance) or because of stiffness of alveolar walls (increased compliance) or both. Thus, ventilation will be maldistributed in a lung unit with abnormal RC time constant, with more ventilation to areas with relatively normal time constant than other areas. A lung unit with a large time constant (i.e. greater resistance and compliance) does not completely fill by the end of inspiration and empties slowly during expiration. In contrast, a lung unit with a small time constant (i.e. smaller resistance and compliance) fills and empties rapidly.

When a lung unit with a large-time constant is located adjacent to a lung unit with a small-time constant, the unit with the large-time constant may withdraw gas from the adjacent lung unit with a short-time constant rather than fresh inspired gas. This “to and fro” behavior is known as pendelluft, and it can occur in abnormal lungs. In addition, a lung unit with a small-time constant may receive a higher proportion of dead space gas, which reduces its alveolar ventilation. This effect is prominent in chronic obstructive lung disease, in which compliant lung units with extremely large-time constants behave essentially as dead space. The higher the respiratory rate, the greater is the discrepancy in filling and emptying between these two kinds of units, and thus greater the inhomogeneity of ventilation.

Another reason for uneven ventilation of small lung units is a gradient of gas concentration along the small airways, a condition called stratified inhomogeneity. Inspired gas reaches near the region of the terminal or respiratory bronchioles by convective flow, but gas flow over the rest of the distance to the alveoli is accomplished primarily by molecular diffusion within the airways. When airway calibers are altered, as in emphysema, the process of gas diffusion may be incomplete for each breath. Thus, alveoli more distal to conducting airways are less well ventilated than proximal alveoli.

Several mechanisms tend to preserve the uniform distribution of ventilation in the lung. One of these mechanisms is the pendelluft phenomenon described earlier. Another mechanism is gas exchange through collateral air channels between adjacent lung units. Collateral ventilation can occur between alveolo-alveolar pores of Kohn, bronchio-alveolar canals of Lambert, and bronchiolo-bronchiolar foramina of Martin. Another factor that tends to improve the uniformity of ventilation is the interdependence of peripheral lung units, which stems from the observation that contiguous lung units are attached integrally to each other by the connective tissue framework of the lung parenchyma. The behavior of one unit must therefore influence the behavior of its neighbors. This framework serves to offset the tendency for regional differences in compliance to make lung units larger or smaller than they should be for optimal performance.

ROLE OF GRAVITY

Gravity also plays some role in the distribution of ventilation. In the upright position, ventilation per unit lung volume is greater at base of lung than at apex. This happens because at the start of inspiration, intrapleural pressure is less negative at base than at apex, and since the intrapulmonary-intrapleural pressure difference is less than at apex, the lung is less expanded. Conversely, at apex, the lung is more expanded, i.e. the percentage of maximum lung volume is greater. Because of stiffness of lung, the increase in lung volume per unit increase in pressure is smaller when the lung is initially more expanded, and ventilation is consequently greater at the base.

The ventilation differences tend to disappear in supine position, and the weight of lung makes the intrapleural pressure lower at the base in the upright position. However, the inequalities of ventilation and blood flow in humans have been found to persist to a remarkable degree in the weightlessness of space. Therefore, other as yet unknown factors apparently also play a role in producing the inequalities. It should also be noted that at very low lung volumes, such as those after forced expiration, intrapleural pressure at lung bases can actually exceed atmospheric pressure in the airways, and the small airways such as respiratory bronchioles collapse (airway closure). In older people and in those with chronic lung disease, some of the elastic recoil is lost, with a resulting decrease in intrapleural pressure. Consequently, airway closure may occur at the bases of lungs in the upright position without forced expiration, at volumes as high as the functional residual capacity.

\[
\begin{align*}
V_D & = \text{total dead space} \\
V_E & = \text{minute ventilation} \\
P_aCO_2 & = \text{partial pressure of carbon dioxide in the expired air} \\
P_aCO_2 & = \text{partial pressure of carbon dioxide in the alveolar air (which in practice is measured by the arterial PCO}_2\text{)}
\end{align*}
\]

The relationship of total and alveolar ventilation was first described by Christian Bohr and is also known as “Bohr dead space”.

Gravity also plays some role in the distribution of ventilation.
PULMONARY CIRCULATION

The circulation of the entire cardiac output through lungs is ideally suited for rapid gas exchange. The pulmonary vascular bed resembles systemic circulation, except that the walls of pulmonary artery and its large branches are about 30% as thick as the wall of the aorta, and the small arterioles, unlike the systemic arterioles, have relatively little muscle in their walls. There is also some smooth muscle in the walls of the postcapillary venules. Also, the pulmonary capillaries are large with multiple anastomoses, so that each alveolus sits in a capillary basket. Blood from the right side of the heart flows through an intricate network of pulmonary capillaries around the alveoli.

After getting oxygenated, blood drains back into the left atrium through four pulmonary veins. The pulmonary bed is characteristically a low-pressure circuit. There is a dense network of capillaries around each alveolus. Rough estimates put the total number of capillaries at about six billion or two thousand capillaries per alveolus. Not all the capillaries are perfused under resting conditions. An increased blood flow due to an increased cardiac output (as much as 25 liters per minute during exercise in contrast to 5–6 liters during resting conditions) can be accommodated easily in pulmonary circulation without an increase in the pulmonary arterial pressure. This is made possible as a result of two major mechanisms that include recruitment, which is the opening of previously unperfused pulmonary capillaries in the upper lung zones, and distension in the entire pulmonary vasculature due to increased transmural pressure gradient. The best example of the ability of pulmonary vasculature to adapt to increased blood flow is following pneumonectomy, when the remaining lung will normally take the entire resting pulmonary blood flow without an increase in pulmonary arterial pressure.

Distribution of Perfusion

The distribution of pulmonary blood flow is nonuniform from apex to base. In upright position, upper portions of the lungs are well above the level of heart, and bases are at or below it. Consequently, there is a relatively marked pressure gradient in the pulmonary arteries from the top to the bottom of the lungs, because of effect of gravity, and a resulting linear increase in pulmonary blood flow from the apices to the bases of the lungs. The following three concepts about pressure in the pulmonary vessels are important to understanding the behavior of the pulmonary circulation.

Intravascular Pressure

This is the blood pressure inside the lumen of the vessel relative to the atmospheric pressure. The pulmonary arterial pressure (P_a) and pulmonary venous pressure (P_v) can be measured directly by placing catheters into the blood stream at specific points, and in clinical practice, capillary pressure can be estimated by wedging a catheter into a lobar branch of pulmonary artery. The “wedge” pressure measured under the conditions of “no flow” reflects the pressure downstream of the next freely communicating channels, that is, pulmonary capillaries or small pulmonary venules.

Transmural Pressure

This is the difference between the pressure inside a vessel and the pressure in the tissue around it. For example, the pressure around the pulmonary arteries and veins is approximately equal to the intrapleural pressure. The pressure around the capillaries is approximately the intra-alveolar pressure (P_A). It is this difference in transmural pressure that leads to the different behavior of alveolar and extra-alveolar vessels under conditions such as lung inflation. At the capillary level, the transmural pressure is also an important determinant of the rate of transudation of fluid across the capillary bed.

Pulmonary Driving Pressure

This is the difference in intravascular pressure between one point in the circulation and another point downstream, and is the pressure involved in overcoming the frictional resistance that impedes blood flow between two points. The driving pressure for the pulmonary circulation is the difference between the intravascular pressure in the main pulmonary artery and that immediately after the pulmonary circulation in the left atrium.

The intravascular pressures of pulmonary circulation are influenced by hydrostatic pressure created by gravity. The alveolar pressures significantly affect the intra-alveolar capillaries. As alveolar pressure is relatively independent of gravity, the relationships among pulmonary arterial, pulmonary venous and alveolar pressures must also influence the distribution of pulmonary blood flow. West subdivided the lung into four zones with differing patterns of blood flow (Fig. 3). In zone 1, near the apex of lung, wherein the alveolar pressure exceeds both pulmonary arterial and venous pressures (P_a > P_A > P_v), and thus the alveolar vessels are collapsed and there is no pulmonary blood flow. In zone 2, the pulmonary arterial pressure exceeds the alveolar pressure, but alveolar pressure exceeds venous pressures (P_a > P_A > P_v). Under these conditions, the resistance to blood flow is determined by the difference between pulmonary arterial and alveolar pressures, rather than by the expected arterial-venous pressure difference. This behavior has been referred to variously as the waterfall or sludge effect. Also in zone 2, blood flow increases progressively down the lung because of the increasing hydrostatic effect on pulmonary arterial pressure, which increases the driving pressure in this region (pulmonary arterial pressure minus alveolar pressure).

In zone 3, the pulmonary venous pressure exceeds alveolar pressures (P_v > P_A > P_a), and blood flow is dependent on the pressure difference between P_v and P_a, and is maximal.
There is also a progressive increase in perfusion because of the progressive "distension" of vessels due to increase in $P_a$ and $P_v$, while $P_A$ remains constant. In *zone 4*, the relationships between intravascular and alveolar pressures are same as in *zone 3*, but the blood flow decreases slightly. *Zone 4* occurs in the lowermost region of the upright human lung and diminishes as lung volume increases. Conversely, as lung volume decreases, this region of reduced blood flow extends farther and farther up the lung, so that at FRC blood flow decreases progressively down the bottom half of the lung. At residual volume, *zone 4* extends nearly all the way up the lung, so that blood flow at the apex exceeds that at the base. This condition cannot be explained by the interactions among the pulmonary arterial, venous and alveolar pressures. Instead, the reduced blood flow in *zone 4* is probably due to the narrowing of extra-alveolar vessels at the lung base that result from lower lung inflation due to airways closing down at the "closing volume". The increased contribution of extra-alveolar vessels to pulmonary vascular resistance results in the presence of a zone of reduced blood flow in that region. *Zone 4* would be expected to increase in the presence of interstitial pulmonary edema, because the edematous fluid increases interstitial pressure in the vascular sheath and thereby narrows the extra-alveolar vessels. This is a plausible mechanism for the inverted distribution of blood flow (cephalization of pulmonary vasculature on chest X-ray) in pulmonary edema.

Not all the inhomogeneity of blood flow in the lung can be explained by gravitational effects. Indirect measurements of inhomogeneity (monitoring the magnitude of cardiogenic oscillations on the expired carbon dioxide tracing) of pulmonary blood flow have been made in astronauts in space shuttles, and a striking reduction in inhomogeneity of blood flow was detected during weightlessness compared with that observed in the upright posture before or after the flight. Interestingly, substantial inhomogeneity of blood flow still remained, indicating that some gravity-independent mechanism was also present. Another situation where the gravitational model fails is the situation of prone position ventilation, where the perfusion is probably more homogeneous and not dependent on gravity.

**DIFFUSION**

Diffusion is the rate at which oxygen from alveolus is transferred across the alveolocapillary barrier to combine with hemoglobin in the red blood cells of pulmonary capillaries. The situation in lungs can be visualized as a two chamber model with different partial pressures of oxygen and a liquid barrier separating the two. The transfer of gases from the alveoli to the capillary blood during the pulmonary transit time of 0.75 seconds depends on their reaction with hemoglobin in the blood. For example, nitrous oxide ($N_2O$) does not react, and reaches equilibrium in about 0.1 seconds. In this situation, the amount of $N_2O$ taken up is not limited by diffusion, but by the amount of blood flowing through the pulmonary capillaries, i.e. it is flow-limited.
On the other hand, carbon monoxide (CO) is taken up by the hemoglobin in the red blood cells at such a high rate that the partial pressure of CO in the capillaries stays very low and equilibrium is not reached in 0.75 seconds till the blood is in the pulmonary capillaries. Therefore, the transfer of CO is not limited by perfusion at rest and instead is diffusion-limited. Oxygen is intermediate between N₂O and CO; it is taken up by hemoglobin, but much less avidly than CO, and it reaches equilibrium with capillary blood in about 0.3 seconds. Thus, its uptake is also perfusion-limited. Diffusing capacity of the lung for a given gas is directly proportionate to the surface area of the alveolo-capillary membrane and inversely proportionate to its thickness. The factors that influence the movement of gas from the area of higher partial pressure (alveolus) to the area of low partial pressure (capillaries) are governed by the Fick’s law:

\[ V = \frac{Ad}{T (P_1 - P_2)} \]

where

- \( V \) = volume of gas diffusing per unit time (mL/minute)
- \( A \) = area available for diffusion (cm²)
- \( P_1 - P_2 \) = pressure difference of gas on two sides (mm Hg)
- \( d \) = diffusion coefficient of the barrier (cm²/minute/mm Hg)

This diffusion coefficient \( d \) is further related to the solubility of the gas within the liquid barrier and the square root of the molecular weight of the gas. Other factors being constant, driving pressure is the most important factor determining flow of oxygen across the alveolo-capillary membrane. When this pressure falls, such as at high altitudes, the oxygen delivery to the tissues becomes diffusion limited. Similarly, diffusion is inversely proportional to the thickness of the membrane.

Although diffusion is reduced in the presence of thickened alveolo-capillary membrane (e.g. interstitial lung disease) or the loss of gas exchange areas (e.g. chronic obstructive airway disease); it is rarely the sole factor responsible for hypoxemia encountered in these conditions. This is because the transfer of oxygen and carbon dioxide is perfusion limited. The normal capillary transit time across the alveolar walls is usually 0.75 seconds, but in healthy individuals only 0.25 seconds is required for gas exchange to be completed. Thus, there is an adequate time for gas exchange to occur even in the presence of a diffusion defect. The gas exchange becomes diffusion dependent during conditions, which increase cardiac output, such as exercise, anxiety, etc. when the capillary transit time is significantly reduced.

**VENTILATION-PERFUSION (V/Q) RELATIONSHIPS**

The ratio of pulmonary ventilation to pulmonary blood flow for the whole lung at rest is about 0.8 to 1 (4-6 L/minute ventilation divided by 5-6 L/minute blood flow), and this matching of distribution of ventilation and perfusion is the most important determinant of gas exchange. The ventilation-perfusion mismatch is the final common pathway to cause hypoxemia in most pulmonary diseases (Fig. 5). An area of lung that is well perfused, but under ventilated acts as a right to left shunt (physiological shunt) whereas an area that is well ventilated, but under perfused acts like a dead space (physiological dead space). The spectrum of V/Q ratios in a healthy lung would vary between zero (perfused, but not ventilated) to infinity (ventilated, but not perfused).

The ideal V/Q ratio of one indicates perfectly matched ventilation and perfusion. Although V/Q mismatch includes both physiologic shunt and physiologic dead space, but in clinical parlance, the term generally denotes physiologic shunt as physiologic dead space is rarely, if ever, the cause of hypoxemia. In an alveolar-capillary unit with a V/Q ratio of 0 (physiologic shunt), the blood leaving the unit has the composition of mixed venous blood entering the pulmonary capillaries, i.e. PO₂ of 40 mm Hg and PCO₂ of 46 mm Hg whereas in an alveolar-capillary unit with a high V/Q ratio (physiologic dead space) the small amount of blood leaving the unit has partial pressures of O₂ and CO₂ are 150 mm Hg and 0 mm Hg approaching the composition of inspired gas.

Because of the sigmoid shape of the oxyhemoglobin dissociation curve, it is important to differentiate between the partial pressure and the content of oxygen in the blood. Hemoglobin is almost fully (> 90%) saturated at a PO₂ of 60 mm Hg, and little additional O₂ is carried by hemoglobin even with a substantial elevation of PO₂ above 60 mm Hg. On the other hand, significant O₂ desaturation of hemoglobin occurs once PO₂ falls below 60 mm Hg and onto the steep descending limb of the curve. As a result, blood coming from regions of the lung with a high V/Q ratio and a high PO₂ has only a small elevation in O₂ content and cannot compensate for blood coming from regions with a low V/Q ratio and a low PO₂ which has a significantly decreased O₂ content. Although V/Q mismatching can influence PCO₂, this effect is
less marked and is often overcome by an increase in overall minute ventilation.

The alveolar $\text{PO}_2$ appears to be the most important factor involved in regulating the distribution of ventilation-perfusion within the lung. In this respect, hypoxic pulmonary vasoconstriction can be considered as part of a negative feedback loop. For example, in lung units with low $V/Q$ ratios, there is a fall in local alveolar $\text{PO}_2$ and constriction of associated microcirculation reduces the local pulmonary blood flow. This tends to restore the local $V/Q$ ratio toward its normal value. This effect can be appreciated in the residents of high altitudes, who are exposed constantly to lower ambient $O_2$ concentrations. Residents of high altitudes have better $V/Q$ matching than sea level residents, as reflected by a smaller alveolar-arterial $\text{PO}_2$ difference.

The intensity of hypoxic pulmonary vasoconstriction varies among different lung regions, and probably depends on the smooth muscle tone in different vessels. More recently, a role for nitric oxide in regulating local ventilation-perfusion matching has been suggested as nitric oxide is a selective pulmonary vasodilator (no systemic effects), and inhibits hypoxic pulmonary vasoconstriction. Theoretically, the inhalation of nitric oxide can cause selective pulmonary vasodilation in adequately ventilated areas and improve gas exchange. The nitric oxide-mediated mechanism may also be important in patients with inflammatory lung diseases, in whom the production of nitric oxide is increased. The loss of local hypoxic vasoconstriction would worsen ventilation-perfusion mismatch.

**CONTROL OF VENTILATION**

The active inspiratory process facilitates expansion of the lungs. It involves contraction of intercostal muscles and diaphragm to move the chest upward and outward. By doing so the intrathoracic and alveolar pressures are lowered and the flow of the air into the lungs is facilitated. Expiration is usually a passive process. The lungs and chest collapse under their own elastic recoil and raise the intrathoracic and alveolar pressures. The air then flows out of the lungs.

Ventilation is controlled tightly through three components—sensors (or receptors), central controllers and effectors (muscles of respiration). The respiratory control mechanisms operate through both neuronal and chemical receptors. While the former are peripherally located (airway, lung, chest wall, blood vessels), the latter are both peripherally and centrally located. Control centers in the brain put together information from all these receptors, and fine-tune the neuronal drive to respiratory musculature, which in turn controls the level of ventilation.

**Neuronal Receptors**

The neuronal receptors vary greatly in their location and response characteristics. Some are rapidly adaptive to change in lung volume or irritation by noxious agents or inflammatory mediators. Receptor signals are mediated through the vagus nerve to the respiratory center, and have variable effects like increase in ventilation, cough and/or bronchoconstriction. Others like stretch receptors or muscle spindles in airway smooth muscles adapt slowly to lung volume changes. These get activated by lung over distension and signal the respiratory center to discontinue the stimulation of the inspiratory muscles, allowing expiration to begin. This response is called the inflation (Herring-Breuer) reflex. Juxtacapillary (or J) receptors located in alveolar walls sense the engorgement of the pulmonary capillaries and cause rapid shallow breathing.

**Peripheral Chemoreceptors**

The main location for peripheral chemoreceptors is in aortic and carotid bodies, although they may be present in other areas as well. Carotid bodies are located bilaterally at the bifurcation of common carotid arteries, and are the major receptors in adult life. They mainly respond to arterial hypoxemia, and to hypercapnia, by transmitting signals to nucleus tractus solitarius through ninth cranial nerve, resulting in hyperventilation. Other chemoreceptors in central nervous system adjust ventilation to maintain acid-base homeostasis. The more important receptors are located near central medullary surface and retrotrapezoid nucleus. These receptors respond to pH changes in the cerebrospinal fluid resulting from the diffusion of carbon dioxide through the blood-brain barrier.

**Respiratory Center**

The various positive and negative signals from all these receptors are integrated at the level of respiratory control centers in the medulla and pons, and result in appropriate modifications in frequency, depth and/or pattern of respiration. The dorsal medullary inspiratory center generates rhythmic neuronal impulses that result in contraction of inspiratory muscles. Exhalation is largely a passive process, though it can be actively controlled through ventral respiratory group of neurons in the medulla. Medullary center is controlled by pontine centers. Pneumotaxic center is located in the dorsal and superior pontine area, and is inhibitory to the medullary ventilatory drive. Apneustic area in the lower pons can stimulate respiration if the pneumotaxic center is blocked, but its function is not well understood.

**Ventilatory Responses**

The ventilatory response to carbon dioxide elevation in blood is largely centrally mediated and results in a proportional increase in ventilation that attempts to correct the anomaly, although normocapnia may not be achieved. Relationship between respiratory minute volume and the alveolar carbon dioxide is essentially linear. The ventilatory response to
hypoxia is not so linear. Although mild hypoxemia increases discharge from the peripheral chemoreceptors, the corresponding hypocapnia from any increase in ventilation, as well as a slight alkalosis from the lesser amount of oxyhemoglobin, prevent any sustained hyperventilation. An increase in minute ventilation is only seen when arterial oxygenation falls substantially. The composite effects of hypoxemia, hypercarbia and acidosis are much more complex.

BIBLIOGRAPHY