NUNN'S APPLIED RESPIRATORY PHYSIOLOGY

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EIGHTH EDITION

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Foreword

It is a great honour to write the foreword for the eighth edition of *Nunn's Applied Respiratory Physiology*. Since publication of the first edition in 1969, *Nunn's Applied Respiratory Physiology* has been the classic textbook on this critical subject. The challenge for any textbook on respiratory physiology has been to present the information in a manner which provides for the changing needs of the reader throughout his or her career. The beginning student learns basic respiratory physiology with a focus on lung mechanics and gas exchange under normal conditions; the more advanced student may be interested in understanding the underlying cellular and molecular mechanisms and the applications of respiratory physiology in abnormal conditions; the clinician needs to understand the impact of altered respiratory physiology on specific disease states. The ideal textbook therefore has the daunting challenge of providing a comprehensive but easily understood approach for all three users. Despite the rapid expansion of knowledge in this field, *Nunn's Applied Respiratory Physiology* has accomplished this task throughout the past five decades. Although encyclopaedic in its scope, the book remains the work of a single author, allowing internal consistency so that interrelated concepts can be readily appreciated by the reader and avoiding unnecessary duplication of material between chapters. The perspective of Andrew Lumb, as both a respiratory physiologist and a clinician, remains a core strength of this work.

This eighth edition maintains the tradition of presenting respiratory physiology in a manner which can be readily understood by students, clinicians and investigators throughout their careers. The book continues the three part approach which was first adopted in the fifth edition and directly corresponds to the three users discussed above. Part 1 on basic principles covers anatomy, mechanics, control of breathing, ventilation, circulation, ventilation-perfusion matching, diffusion, carbon dioxide, oxygen and nonrespiratory functions of the lung. The complexity of respiratory physiology is fully covered, and the new colour diagrams significantly improve the ability of readers to understand the underlying concepts despite the mathematical approach. Part 2, applied physiology, discusses the effects of pregnancy, exercise, sleep, altitude, pressure, drowning, smoking, air pollution, anesthesia, hypocapnia, hypercarbia, hypoxia, hyperoxia, anemia and comparative respiratory physiology. The relationship between molecular processes, cellular physiology and resulting blood gases are superbly integrated. A new chapter on comparative physiology has been added, and the comparison of human respiratory physiology to that of other organisms provides a deeper understanding of the underlying principles. Part 3, physiology of pulmonary disease, discusses specific clinical disorders (ventilatory failure, airways disease, pulmonary vascular disease, parenchymal lung disease and acute lung injury), ventilatory support and pulmonary surgery. These chapters have been extensively updated as new information has entered the literature in all these areas. The sections on lung imaging, obesity and respiratory surgery have all markedly expanded, and the book provides an up-to-date presentation in all the relevant clinical areas. Valuable changes which were made in prior editions, such as the key points section of each chapter, have been continued, and new improvements, such as key references, have been added. Finally, the book includes free access to important online materials, including interactive figures, additional chapters and self-assessment questions.

For more than four decades, *Nunn's Applied Respiratory Physiology* has been the standard text for understanding this challenging but critical subject. I congratulate Dr. Lumb on continuing this tradition with a superb new edition which again deserves a place on the bookshelves of students, researchers and clinicians interested in understanding normal respiratory physiology and in treating patients with respiratory disorders.

Ronald G. Pearl

Preface to the Eighth Edition

Over the past 46 years *Nunn's Applied Respiratory Physiology* has developed into a renowned textbook on respiration, providing both physiologists and clinicians with a unique fusion of underlying principles and their applications. With Dr John Nunn's retirement in 1991 a new author was required, and, as Dr Nunn's final research fellow in the Clinical Research Centre in Harrow, I was honoured to be chosen as his successor. As a practising clinician with a fascination for physiology, the eighth edition has again focussed on combining a clear, logical and comprehensive account of basic respiratory physiology with a wide range of applications, both physiological and clinical. This approach acknowledges the popularity of the book among doctors from many medical specialties and will hopefully provide readers with a scientific background with an even greater insight into the applications of respiratory physiology. Clinical chapters in Part 3 of the book are not intended to be comprehensive reviews of the pulmonary diseases considered, but in each case they provide a detailed description of the physiological changes that occur, accompanied by a brief account of the clinical features and treatment of the disease.

Key references are identified by an asterisk in the reference list following each chapter. These references are highlighted because they either provide outstanding recent reviews of their subject or describe research that has had a major impact on the topic under consideration.

Advances in respiratory physiology since the last edition are too numerous to mention individually. Major developments in physiological imaging techniques continue, with the regional ventilation and perfusion of the human lung now visualized in detail and under various physiological circumstances, such as in different body positions (Figure 7.7), at varied lung volumes (Figure 7.5), during hypoxia (Figure 6.9), and with asthma (Figure 27.1). New molecular pathways involved in lung disease continue to be discovered, with the part played by airway epithelial cells becoming increasingly recognized. Other new topics for this edition include respiratory physiotherapy, with an outline in Chapter 31 of the aims, techniques, and underlying physiology of this important intervention for managing many lung diseases. In keeping with its increasing worldwide prevalence, the effects of severe obesity on the respiratory system are now covered in more detail in multiple chapters. This includes the 'obesity paradox' in which some patients with lung disease seem to have a survival advantage from being obese.

Chapter 25, Comparative Respiratory Physiology, is new for this edition and begins by briefly describing the many strategies used by the myriad members of the animal kingdom to overcome the challenge of respiration. The theoretical designs of systems for both aquatic and aerial breathing are outlined along with the varied techniques used for transporting respiratory gases within an organism. The systems described are then illustrated with many examples from the major phyla of the animal kingdom, all the way from microorganisms, through marine invertebrates, crustacea and fish to the air breathing insects, reptiles, birds and mammals. The respiratory systems of some physiological 'elite' animals are also described, such as exercising horses, diving mammals and high-altitude llamas, allowing the reader to see in a wider context the rather ineffective human responses to these situations. Finally, as for the human diseases covered in Part 3, the pathophysiology of common respiratory problems seen in veterinary practice is outlined.

Other major changes for this edition include the move to full colour print, which has enhanced the figures greatly, allowing a much clearer portrayal of the concepts described, for example, the colour change of blood flowing across the lung as it becomes oxygenated. The book is also now available as a print and electronic package for the first time. All print purchasers receive the enhanced eBook version, which can be used online or downloaded to their device for convenient, any time access. It gives readers the flexibility of rapid search across the complete text or the option to review just individual chapters or the handy chapter summaries. There are also interactive figures and extra e-only chapters, as well as new self-assessment material to check

understanding or help prepare for approaching exams.

I wish to personally thank the many people who have helped with the preparation of the book, including my niece Katherine for her veterinary expertise in Chapter 25, and the numerous colleagues who have assisted me in my acquisition of knowledge in subjects not so close to my own areas of expertise. I am indebted to Professor Pearl for his kind words in the Foreword, and would like to thank Osamu Ohtani, Christoph Dehnert, Susan Hopkins, Kenneth Olson and Grace Parraga for providing me with the excellent images used in Figures 1.10, 6.9, 7.5, 25.5 and 27.1, respectively. Last, but by no means least, I would like to thank Lorraine, Emma and Jenny for again tolerating a preoccupied and reclusive husband/father for so long. Jenny, when aged 5, often enquired about my activities in the study, until one evening she nicely summarized my years of work by confidently informing me that 'if you don't breathe, you die'. So what were the other 512 pages about?

Andrew Lumb
Leeds 2016

CHAPTER 1

Functional Anatomy of the Respiratory Tract

KEY POINTS

- In addition to conducting air to and from the lungs, the nose, mouth and pharynx have other important functions including speech, swallowing and airway protection.
- Starting at the trachea, the airway divides about 23 times, terminating in an estimated 30 000 pulmonary acini, each containing more than 10 000 alveoli.
- The alveolar wall is ideally designed to provide the minimal physical barrier to gas transfer, whilst also being structurally strong enough to resist the large mechanical forces applied to the lung.

This chapter is not a comprehensive account of respiratory anatomy but concentrates on those aspects that are most relevant to an understanding of function. The respiratory muscles are covered in Chapter 5.

MOUTH, NOSE AND PHARYNX

Breathing is normally possible through either the nose or the mouth, the two alternative air passages converging in the oropharynx. Nasal breathing is the norm and has two major advantages over mouth breathing: filtration of particulate matter by the vibrissae hairs and better humidification of inspired gas. Humidification by the nose is highly efficient because the nasal septum and turbinates greatly increase the surface area of mucosa available for evaporation and produce turbulent flow, increasing contact between the mucosa and air. However, the nose may offer more resistance to airflow than the mouth, particularly when obstructed by polyps, adenoids or congestion of the nasal mucosa. Nasal resistance may make oral breathing obligatory, and many children and adults breathe only or partly through their mouths at rest. With increasing levels of exercise in normal adults, the respiratory minute volume increases, and at a level of ~35 L/min^{-1} the oral airway comes into play. Deflection of gas into either the nasal or the oral route is under voluntary control and accomplished with the soft palate, tongue and lips. These functions are best considered in relation to a midline sagittal section (Fig. 1.1).

Figure 1.1, *A*, shows the normal position for nose breathing: the mouth is closed by occlusion of the lips, and the tongue is lying against the hard palate. The soft palate is clear of the posterior pharyngeal wall. Figure 1.1, *B*, shows forced mouth breathing, for instance, when blowing through the mouth without pinching the nose. The soft palate becomes rigid and is arched upwards and backwards by contraction of tensor and levator palati to lie against a band of the superior constrictor of the pharynx known as Passavant's ridge which, together with the soft palate, forms the palatopharyngeal sphincter. Note also that the orifices of the pharyngotympanic (Eustachian) tubes lie above the palatopharyngeal sphincter and can be inflated by the subject only when the nose is pinched. As the mouth pressure is raised, this tends to force the soft palate against the posterior pharyngeal wall to act as a valve. The combined palatopharyngeal sphincter and valvular action of the soft palate is very strong and can easily withstand mouth pressures in excess of 10 kPa (100 cmH_2O).

Figure 1.1, *C*, shows the occlusion of the respiratory tract during a Valsalva manoeuvre. The airway is occluded at many sites: the lips are closed, the tongue is in contact with the hard palate anteriorly, the palatopharyngeal sphincter is tightly closed, the epiglottis is in contact with the posterior pharyngeal wall and the vocal folds are closed becoming visible in the midline in the figure.

During swallowing the nasopharynx is occluded by contraction of both tensor and levator palati. The larynx is elevated 2 to 3 cm by contraction of the infrahyoid muscles, stylopharyngeus and palatopharyngeus, coming

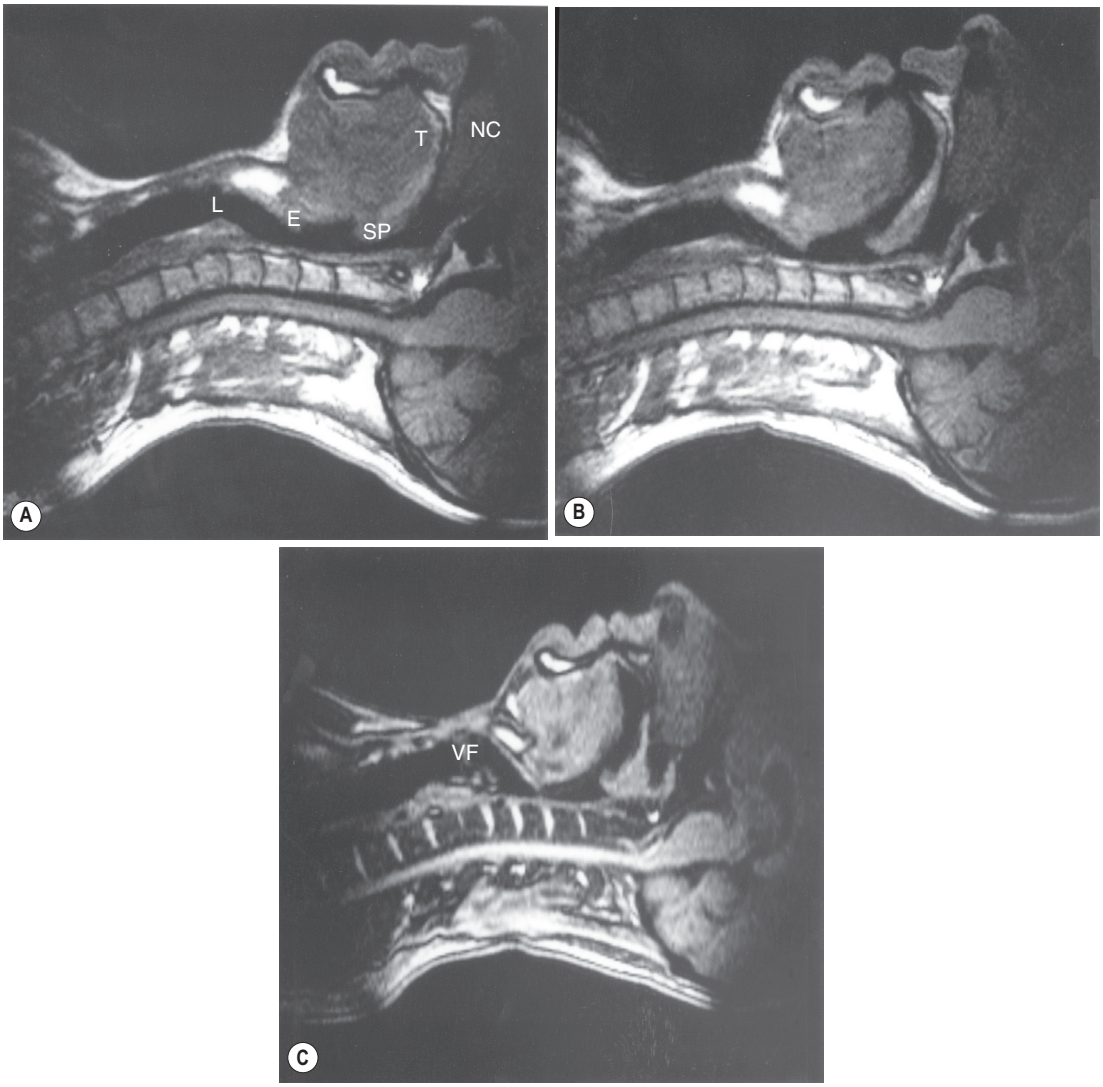

FIG. 1.1 ■ MRI scans showing median sagittal sections of the pharynx in a normal subject. **A,** Normal nasal breathing with the oral airway occluded by lips and tongue. **B,** Deliberate oral breathing with the nasal airway occluded by elevation and backwards movement of the soft palate. **C,** A Valsalva manoeuvre in which the subject deliberately tries to exhale against a closed airway. Data acquisition for scans **(A)** and **(B)** took 45 s so anatomical differences between inspiration and expiration will not be visible. I am indebted to Professor M. Bellamy for being the subject. NC, nasal cavity; T, tongue; SP, soft palate; E, epiglottis; VF, vocal fold; L, larynx.

to lie under the epiglottis. In addition, the aryepiglottic folds are approximated causing total occlusion of the entrance to the larynx. This extremely effective protection of the larynx is capable of withstanding pharyngeal pressures as high as 80 kPa (600 mmHg) which may be generated during swallowing.

Upper airway cross-sectional areas can be estimated from conventional radiographs, magnetic resonance imaging (MRI) as in Figure 1.1 or acoustic pharyngometry. In the latter technique, a single sound pulse of 100 μs duration is generated within the apparatus and passes along the airway of the subject. Recording of the timing and frequency of sound waves reflected back from the airway allows calculation of cross-sectional area which is then presented as a function of the distance travelled along the airway[1] (Fig. 1.2). Acoustic pharyngometry measurements correlate well with MRI scans of the airway,[2] and the technique is now sufficiently developed for use in clinical situations with real-time results. For example, acoustic pharyngometry has been used after the placement of a tracheal tube to differentiate between oesophageal and tracheal intubation,[3] and to estimate

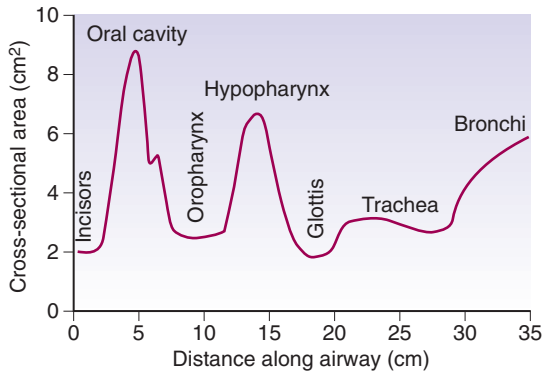

FIG. 1.2 ■ Normal acoustic reflectometry pattern of airway cross-sectional area during mouth breathing.[1,2]

airway size in patients with sleep-disordered breathing (Chapter 14).[4]

THE LARYNX

The larynx evolved in the lungfish for the protection of the airway during such activities as feeding and perfusion of the gills with water. Although protection of the airway remains important, the larynx now has many other functions, all involving some degree of laryngeal occlusion.

Speech

Phonation, the laryngeal component of speech, requires a combination of changes in position, tension and mass of the vocal folds (cords). Rotation of the arytenoid cartilages by the posterior cricoarytenoid muscles opens the vocal folds, while contraction of the lateral cricoarytenoid and oblique arytenoid muscles opposes this. With the vocal folds almost closed, the respiratory muscles generate a positive pressure of 5 to 35 cmH_2O which may then be released by slight opening of the vocal folds to produce sound waves. The cricothyroid muscle tilts the cricoid and arytenoid cartilages backwards and also moves them posteriorly in relation to the thyroid cartilage. This produces up to 50% elongation and therefore tensioning of the vocal folds, an action opposed by the thyroarytenoid muscles, which draw the arytenoid cartilages forwards towards the thyroid shortening and relaxing the vocal folds. Tensioning of the folds results in both transverse and longitudinal resonance of the vocal fold allowing the formation of complex sound waves. The deeper fibres of the thyroarytenoids comprise the vocales muscles, which exert fine control over pitch of the voice by slight variations in both the tension and mass of the vocal folds. A more dramatic example of the effect of vocal fold mass on voice production occurs with inflammation of the laryngeal mucosa and the resulting hoarse voice or complete inability to phonate.

Effort Closure

Tighter occlusion of the larynx, known as effort closure, is required for making expulsive efforts. It is also needed to lock the thoracic cage securing the origin of the muscles of the upper arm arising from the rib cage, thus increasing the power which can be transmitted to the arm. In addition to simple apposition of the vocal folds described previously, the aryepiglottic muscles and their continuation, the oblique and transverse arytenoids act as a powerful sphincter capable of closing the inlet of the larynx by bringing the aryepiglottic folds tightly together. The full process enables the larynx to withstand the highest pressures which can be generated in the thorax, usually at least 12 kPa (120 cmH_2O) and often more. Sudden release of the obstruction is essential for effective coughing (page 56), when the linear velocity of air through the larynx is said to approach the speed of sound.

Laryngeal muscles are involved in controlling airway resistance, particularly during expiration, and this aspect of vocal fold function is described in Chapter 5.

THE TRACHEOBRONCHIAL TREE

An accurate and complete model of the branching pattern of the human bronchial tree remains elusive, although several different models have been described. The most useful and widely accepted approach remains that of Weibel[5] who numbered successive generations of air passages from the trachea (generation 0) down to alveolar sacs (generation 23). This 'regular dichotomy' model assumes that each bronchus regularly divides into two approximately equal size daughter bronchi. As a rough approximation it may therefore be assumed that the number of passages in each generation is double that in the previous generation, and the number of air passages in each generation is approximately indicated by the number 2 raised to the power of the generation number. This formula indicates one trachea, two main bronchi, four lobar bronchi, 16 segmental bronchi, etc. However, this mathematical relationship is unlikely to be true in

practice where bronchus length is variable, pairs of daughter bronchi are often unequal in size and trifurcations may occur.

Work using computed tomography to reconstruct, in three dimensions, the branching pattern of the airways has shown that a regular dichotomy system does occur for at least the first six generations.[6] Beyond this point, the same study demonstrated trifurcation of some bronchi and airways that terminated at generation 8. Table 1.1 traces the characteristics of progressive generations of airways in the respiratory tract.

Trachea (Generation 0)

The adult trachea has a mean diameter of 1.8 cm and length of 11 cm. Anteriorly it comprises a row of U-shaped cartilages which are joined posteriorly by a fibrous membrane incorporating the trachealis muscle (Fig. 1.3). The part of the trachea in the neck is not subjected to intrathoracic pressure changes, but it is very vulnerable to pressures arising in the neck due, for example, to tumours or haematoma formation. An external pressure of the order of 4 kPa (40 cmH_2O) is sufficient to occlude the trachea. Within the chest, the trachea can be compressed by raised intrathoracic pressure during, for example, a cough, when the decreased diameter increases the linear velocity of gas flow and therefore the efficiency of removal of secretions (page 56).

Main, Lobar and Segmental Bronchi (Generations 1 to 4)

The trachea bifurcates asymmetrically, and the right bronchus is wider and makes a smaller angle with the long axis of the trachea. Foreign bodies therefore tend to enter the right bronchus in preference to the left. Main, lobar and segmental bronchi have firm cartilaginous support in their walls, U shaped in the main bronchi, but in the form of irregularly shaped and helical plates lower down with bronchial muscle between. Bronchi in this group (down to generation 4) are sufficiently regular to be individually named (Fig. 1.4). Total cross-sectional area of the respiratory tract is minimal at the third generation (Fig. 1.5).

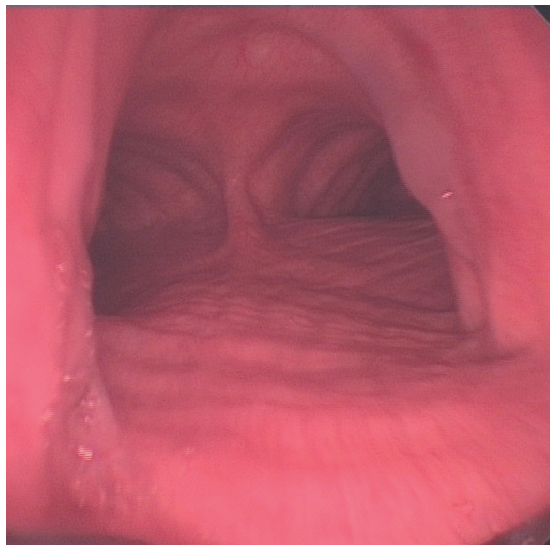

FIG. 1.3 ■ The normal trachea as viewed during a rigid bronchoscopy (page 480). The ridges of the cartilage rings are seen anteriorly and the longitudinal fibres of the trachealis muscle are seen posteriorly, dividing at the carina and continuing down both right and left main bronchi. The less acute angle of the right main bronchus from the trachea can be seen, with its lumen clearly visible, illustrating why inhaled objects preferentially enter the right lung.

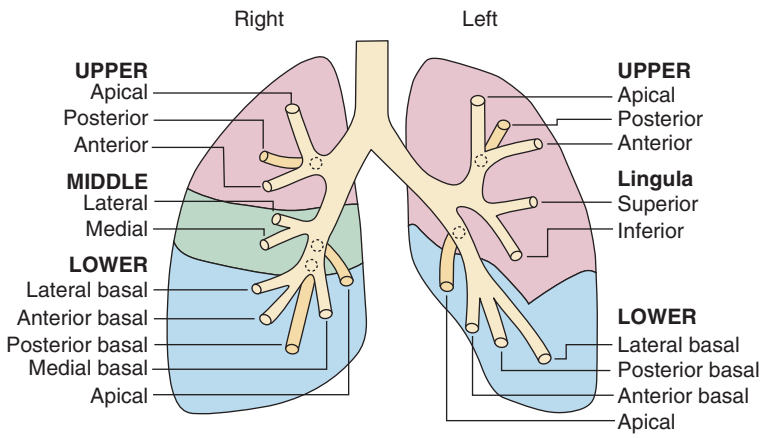

FIG. 1.4 ■ Lobes and bronchopulmonary segments of the lungs. *Red,* upper lobes; *blue,* lower lobes; *green,* right middle lobe. The 19 major lung segments are labelled.

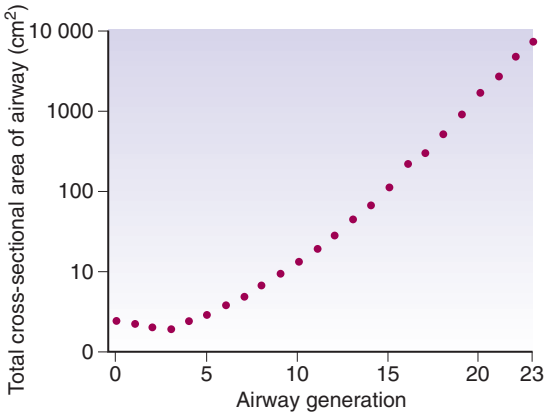

FIG. 1.5 ■ The total cross-sectional area of the air passages at different generations of the airways. Note that the minimum cross-sectional area is at generation 3 (lobar to segmental bronchi). The total cross-sectional area becomes very large in the smaller air passages, approaching a square metre in the alveolar ducts.

These bronchi are subjected to the full effect of changes in intrathoracic pressure and will collapse when the intrathoracic pressure exceeds the intraluminar pressure by ~5 kPa (50 cmH_2O). This occurs in the larger bronchi during a forced expiration, limiting peak expiratory flow rate (see Fig. 3.7).

Small Bronchi (Generations 5 to 11)

The small bronchi extend through about seven generations with their diameter progressively falling from 3.5 to 1 mm. Down to the level of the smallest true bronchi, air passages lie in close proximity to branches of the pulmonary artery in a sheath containing pulmonary lymphatics, which can be distended with oedema fluid giving rise to the characteristic 'cuffing' responsible for the earliest radiographic changes in pulmonary oedema. Because these air passages are not directly attached to the lung parenchyma they are not subject to direct traction and rely for their patency on cartilage within their walls and on the transmural pressure gradient, which is normally positive from lumen to intrathoracic space. In the normal subject this pressure gradient is seldom reversed and, even during a forced expiration, the intraluminar pressure in the small bronchi rapidly rises to more than 80% of the alveolar pressure, which is more than the extramural (intrathoracic) pressure.

Bronchioles (Generations 12 to 14)

An important change occurs at about the eleventh generation where the internal diameter is ~1 mm. Cartilage disappears from the airway wall below this level and ceases to be a factor in maintaining patency. However, beyond this level the air passages are directly embedded in the lung parenchyma, the elastic recoil of which holds the air passages open like the guy ropes of a tent. Therefore the calibre of the airways beyond the eleventh generation is mainly influenced by lung volume because the forces holding their lumina open are stronger at higher lung volumes. The converse of this factor causes airway closure at reduced lung volume (see Chapter 3). In succeeding generations, the number of bronchioles increases far more rapidly than the calibre diminishes (Table 1.1). Therefore the total cross-sectional area increases until, in the terminal bronchioles, it is about 100 times the area at the level of the large bronchi (Fig. 1.5). Thus the flow resistance of these smaller air passages (less than 2 mm diameter) is negligible under normal conditions. However, the resistance of the bronchioles can increase to very high values when their strong helical muscular bands are contracted by the mechanisms described in Chapters 3 and 27. Down to the terminal bronchiole the air passages are referred to as conducting airways, which derive their nutrition from the bronchial circulation and are thus influenced by systemic arterial blood gas levels. Beyond this point the smaller air passages are referred to as acinar airways and rely upon the pulmonary circulation for their nutrition.

Respiratory Bronchioles (Generations 15 to 18)

Down to the smallest bronchioles, the functions of the air passages are solely conduction and humidification. Beyond this point there is a gradual transition from conduction to gas exchange. In the four generations of respiratory bronchioles there is a gradual increase in the number of alveoli in their walls. Like the bronchioles, the respiratory bronchioles are embedded in lung parenchyma; however, they have a well-defined muscle layer with bands which loop over the opening of the alveolar ducts and the mouths of the mural alveoli. There is no significant change in calibre of advancing generations of respiratory bronchioles (~0.4 mm diameter).

Alveolar Ducts (Generations 19 to 22)

Alveolar ducts arise from the terminal respiratory bronchiole, from which they differ by

TABLE 1.1 **Structural Characteristics of the Air Passages**[7]

		Generation	Number	Mean Diameter (mm)	Area Supplied	Cartilage	Muscle	Nutrition	Emplacement	Epithelium
Trachea	Conducting airways	0	1	18	Both lungs	U shaped	Links open end of cartilage			Columnar ciliated epithelium
Main bronchi		1	2	12	Individual lungs			From the bronchial circulation	Within connective tissue sheath alongside arterial vessels	
Lobar bronchi		2 ↓ 3	4 ↓ 8	8 ↓ 5	Lobes	Irregular shaped	Helical bands			
Segmental bronchi		4	16	4	Segments					
Small bronchi		5 ↓ 11	32 ↓ 2000	3 ↓ 1	Secondary lobules					
Bronchioles Terminal bronchioles		12 ↓ 14	4000 ↓ 16,000	1 ↓ 0.7	Pulmonary acinus	Absent	Strong helical muscle bands		Embedded directly in the lung parenchyma	Cuboidal
Respiratory bronchioles	Acinar airways	15 ↓ 18	32,000 ↓ 260,000	0.4			Muscle bands between alveoli	From the pulmonary circulation		Cuboidal to flat between alveoli
Alveolar ducts		19 ↓ 22	520,000 ↓ 4,000,000	0.3			Thin bands in alveolar septa		Form the lung parenchyma	Alveolar epithelium
Alveoli		23	8,000,000	0.2						

having no walls other than the mouths of mural alveoli (approximately 20 in number). The alveolar septa comprise a series of rings forming the walls of the alveolar ducts and containing smooth muscle. Approximately 35% of the alveolar gas resides in the alveolar ducts and the alveoli that arise directly from them.

Alveolar Sacs (Generation 23)

The last generation of the air passages differs from alveolar ducts solely because they are blind. It is estimated that about 17 alveoli arise from each alveolar sac and account for about half of the total number of alveoli.

Pulmonary Acinus

A pulmonary acinus is usually defined as the region of lung supplied by a first-order respiratory bronchiole and includes the respiratory bronchioles, alveolar ducts and alveolar sacs distal to a single terminal bronchiole (Fig. 1.6). This represents the aforementioned generations 15 to 23, but in practice the number of generations within a single acinus is quite variable being between 6 and 12 divisions beyond the terminal bronchiole. A human lung contains about 30 000 acini,[7] each with a diameter of ~3.5 mm and containing in excess of 10 000 alveoli. A single pulmonary acinus is probably the equivalent of the alveolus when it is considered from a functional standpoint as gas movement within the acinus when breathing at rest is by diffusion rather than tidal ventilation. Acinar morphometry therefore becomes crucial,[8] in particular the path length between the start of the acinus and the most distal alveolus which in humans is between 5 and 12 mm.[7]

Respiratory Epithelium[9]

Before inspired air reaches the alveoli it must be humidified, and airborne particles, pathogens and irritant chemicals removed. These tasks are undertaken by the respiratory epithelium and its overlying layer of airway lining fluid, and are described in Chapter 11. To facilitate these functions the respiratory epithelium contains numerous cell types.

Ciliated Epithelial Cells[10]

These are the most abundant cell type in the respiratory epithelium. In the nose, pharynx and larger airways the epithelial cells are pseudostratified, gradually changing to a single layer of columnar cells in bronchi, cuboidal cells in

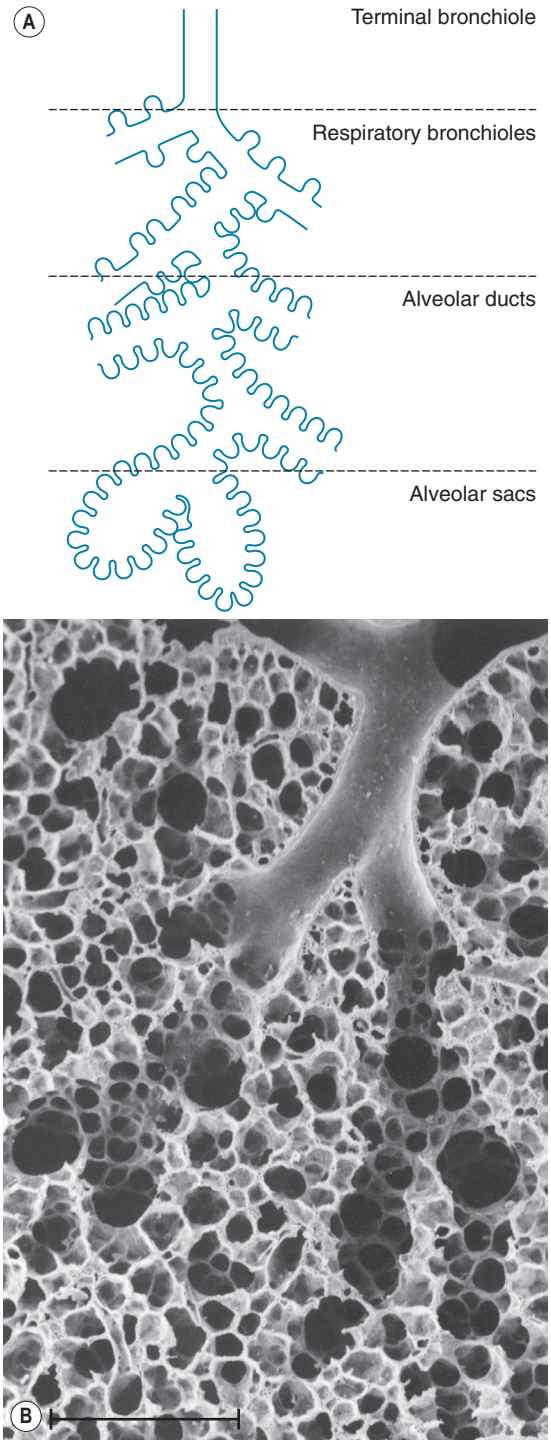

FIG. 1.6 ■ **A,** Schematic diagram of a single pulmonary acinus showing four generations between the terminal bronchiole and the alveolar sacs. The average number of generations in human lung is eight, but may be as many as 12. **B,** Section of rabbit lung showing respiratory bronchioles leading to alveolar ducts and sacs. Human alveoli would be considerably larger. Scale bar = 0.5 mm. (Photograph kindly supplied by Professor E. R. Weibel.)

bronchioles, and finally thinning further to merge with the type I alveolar epithelial cells (see later). They are differentiated from either basal or secretory cells (see later) and are characterized by the presence of around 300 cilia per cell (page 204). The ratio of secretory to ciliated cells in the airway decreases in more distal airways from about equal in the trachea to almost three-quarters ciliated in the bronchioles.

Goblet Cells[11]

These are present at a density of approximately 6000 per mm^2 (in the trachea) and are responsible for producing the thick layer of mucus that lines all but the smallest conducting airways (page 204).

Submucosal Secretory Cells

Submucosal glands occur in the larger bronchi and in the trachea; in the latter there are about 10 submucosal openings per mm^2. The glands comprise both serous cells and mucous cells, with serous cells occurring in the gland acinus, whereas mucous cells are found closer to the collecting duct. The serous cells have the highest levels of membrane-bound cystic fibrosis transmembrane conductance regulator in the lung (Chapter 27).

Basal Cells

These cells lie underneath the columnar cells giving rise to the pseudostratified appearance and are absent in the bronchioles and beyond. They are the stem cell responsible for producing new epithelial and goblet cells.

Mast Cells

The lungs contain numerous mast cells which are located underneath the epithelial cells of the airways and in the alveolar septa. Some also lie free in the lumen of the airways and may be recovered by bronchial lavage. Their important role in bronchoconstriction is described in Chapter 27.

Nonciliated Bronchiolar Epithelial (Clara) Cells

These cells are found in the mucosa of the terminal bronchioles where they may be the precursor of epithelial cells in the absence of basal cells. They are metabolically active,[12] secreting surfactant proteins A, B and D (page 19), antiprotease enzymes and a variety of other proteins of uncertain function.

Neuroepithelial Cells

These cells are found throughout the bronchial tree, but occur in larger numbers in the terminal bronchioles. They may be found individually or in clusters as neuroepithelial bodies and are of uncertain function in the adult lung. Present in foetal lung tissue in a greater number they may have a role in controlling lung development. Similar cells elsewhere in the body secrete a variety of amines and peptides such as calcitonin, gastrin releasing peptide, calcitonin gene-related peptide and serotonin.

THE ALVEOLI

The mean total number of alveoli has been estimated as 400 million, but ranges from about 270 to 790 million, correlating with the height of the subject and total lung volume.[13,14] The size of the alveoli is dependent on lung volume but due to gravity they are normally larger in the upper part of the lung, except at maximal inflation when the vertical gradient in size disappears. At functional residual capacity the mean diameter of a single alveolus is 0.2 mm and the total surface area of the alveoli is ~130 m^2.

The Alveolar Septa

The septa are under tension generated partly by collagen and elastin fibres, but more by surface tension at the air–fluid interface (page 17). They are therefore generally flat, making the alveoli polyhedral rather than spherical. The septa are perforated by small fenestrations known as the pores of Kohn (Fig. 1.7)[15], which provide collateral ventilation between alveoli. Collateral ventilation also occurs between small bronchioles and neighbouring alveoli, adjacent pulmonary acini and occasionally intersegmental communications,[16] and is more pronounced in patients with emphysema (page 398) and in many other species of mammal (page 370).

On one side of the alveolar wall the capillary endothelium and the alveolar epithelium are closely apposed, with almost no interstitial space, such that the total thickness from gas to blood is ~0.3 μm (Figs 1.8 and 1.9)[17]. This may be considered the 'active' side of the capillary and gas exchange must be more efficient on this side. The other side of the capillary, which may be considered the 'service' side, is usually more than 1- to 2-μm thick and contains a recognisable

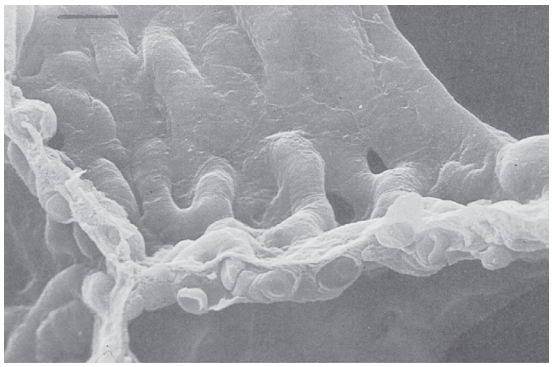

FIG. 1.7 ■ Scanning electron micrograph of the junction of three alveolar septa which are shown in both surface view and section showing the polyhedral structure. Two pores of Kohn are seen to the right of centre. Red blood cells are seen in the cut ends of the capillaries. Scale bar = 10 μm. (Reproduced from reference 15 by permission of the author and the publishers; © Harvard University Press.)

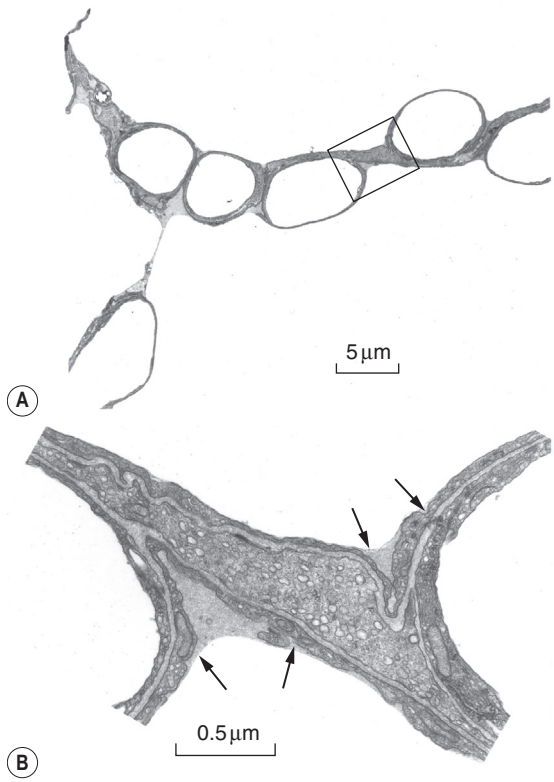

FIG. 1.9 ■ **A,** Transmission electron micrograph of alveolar septum with lung inflated to 40% of total lung capacity. The section in the box is enlarged in **(B)** to show alveolar lining fluid, which has pooled in two concavities of the alveolar epithelium and has also spanned the pore of Kohn in **(A)**. There is a thin film of osmiophilic material *(arrows),* probably surfactant, at the interface between air and the alveolar lining fluid. (Reproduced from reference 17 by permission of the authors and the editors of *Journal of Applied Physiology*.)

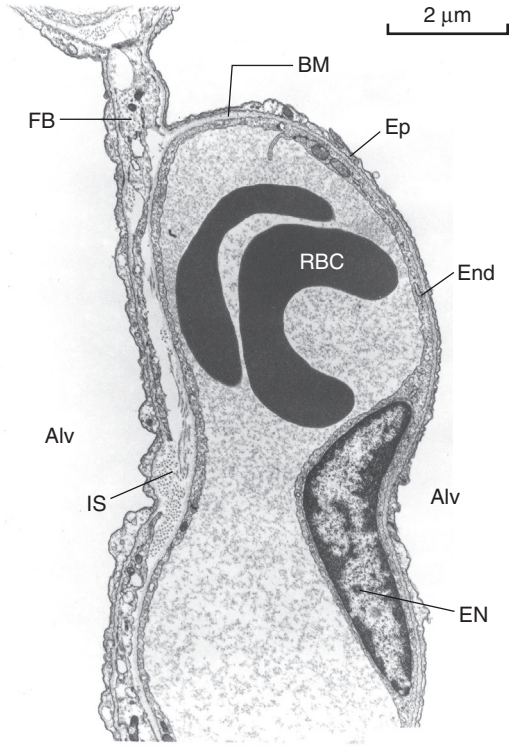

FIG. 1.8 ■ Details of the interstitial space, the capillary endothelium and alveolar epithelium. Thickening of the interstitial space is confined to the left of the capillary (the service side) whereas the total alveolar/capillary membrane remains thin on the right (the active side) except where it is thickened by the endothelial nucleus. Alv, alveolus; BM, basement membrane; EN endothelial nucleus; End, endothelium; Ep, epithelium; FB, fibroblast process; IS, interstitial space; RBC, red blood cell. (Electron micrograph kindly supplied by Professor E. R. Weibel.)

interstitial space containing elastin and collagen fibres, nerve endings and occasional migrant polymorphs and macrophages. The distinction between the two sides of the capillary has considerable pathophysiological significance as the active side tends to be spared in the accumulation of both oedema fluid and fibrous tissue (Chapter 28).

The Fibre Scaffold[18]

The connective tissue scaffold which forms the lung structure has three interconnected types of fibre:

1. Axial spiral fibres running from the hilum along the length of the airways
2. Peripheral fibres originating in the visceral pleura and spreading inwards into the lung tissue

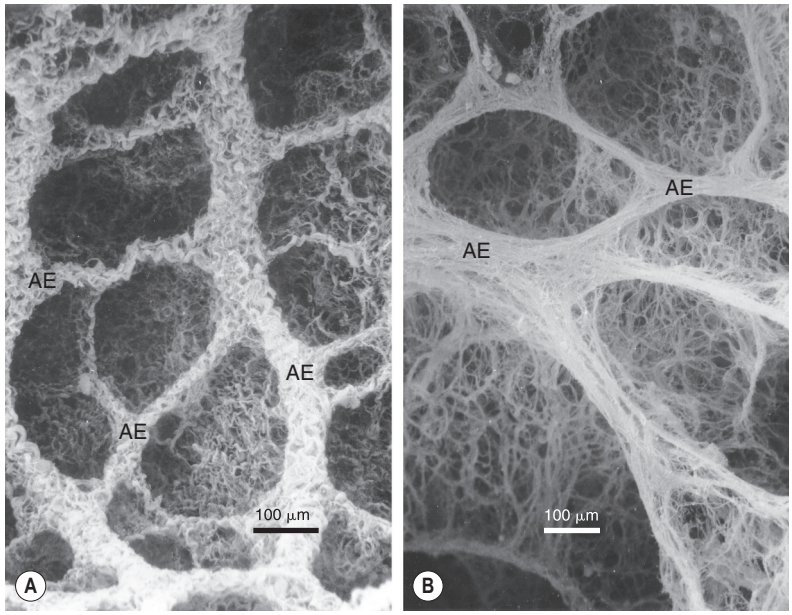

FIG. 1.10 ■ Electron micrographs of the collagen fibre network of rat lung at low lung volume **(A)** and when fully inflated **(B)**.[19] Note the folded, zigzag shape of the collagen at low lung volume in **(A)**. (Photograph kindly supplied by Professor Ohtani. Reproduced by permission of *Archives of Histology and Cytology*.)

3. Septal fibres, a network of which forms a basket-like structure[19] of alveolar septa, through which are threaded the pulmonary capillaries, which are themselves a network

As a result, capillaries pass repeatedly from one side of the fibre scaffold to the other (Fig. 1.7), the fibre always residing on the thick (or service) side of the capillary allowing the other side to bulge into the lumen of the alveolus. The left side of the capillary in Figure 1.8 is the side with the fibres. Structural integrity of the whole fibre scaffold is believed to be maintained by the individual fibres being under tension, referred to as a *tensegrity structure*,[18] such that when any fibres are damaged, the alveolar septum disintegrates and adjacent alveoli change shape, ultimately leading to emphysema (page 397).[20]

How the shape of this complex structure changes with breathing remains uncertain.[21] Increasing lung volume may be achieved by increasing the size of alveolar ducts, expanding alveoli or by recruitment of previously collapsed alveoli. All three undoubtedly contribute as lung volume increases approximately fivefold from residual volume to total lung capacity (page 26). Recent work using a new imaging technique demonstrated only small changes in alveolar size at different lung volumes but a large change in alveolar numbers, indicating recruitment as the main mechanism for increasing lung volume.[14,21] Change in alveolar size is facilitated by the molecular structures of both the elastin and collagen that make up the fibre scaffold, with the collagen forming helices or zigzags at lower lung volumes (Fig. 1.10).[19]

At the cellular level, the scaffolding for the alveolar septa is provided by the basement membrane, which provides the blood–gas barrier with enough strength to withstand the enormous forces applied to lung tissue.[22,23] At the centre of the basement membrane is a layer of type IV collagen, the lamina densa, ~50 nm thick and made up of many layers of a diamond-shaped matrix of collagen molecules. On each side of the lamina densa the collagen layer is attached to the alveolar or endothelial cells by a series of proteins collectively known as laminins, of which seven subtypes are now known. The laminins are more than simple structural molecules, having complex interactions with membrane proteins and the intracellular cytoskeleton[24] to help regulate cell shape and permeability, etc. These aspects of the function of the basement membrane are important. It has been shown that increases in the capillary transmural pressure gradient greater than ~3 kPa (30 cmH_2O) may cause disruption of endothelium and/or epithelium, whereas the basement membrane tends to remain intact, sometimes as the only remaining separation between blood and gas.[25]

ALVEOLAR CELL TYPES

Capillary Endothelial Cells

These cells are continuous with the endothelium of the general circulation and, in the pulmonary capillary bed, have a thickness of only 0.1 μm except where expanded to contain nuclei (Fig. 1.8). Electron microscopy shows the flat parts of the cytoplasm are devoid of all organelles except for small vacuoles (caveolae or plasmalemmal vesicles) which may open onto the basement membrane or the lumen of the capillary or be entirely contained within the cytoplasm (see Fig. 1.9). The endothelial cells abut against one another at fairly loose junctions of the order of 5 nm wide.[26] These junctions permit the passage of quite large molecules, and the pulmonary lymph contains albumin at about half the concentration in plasma. Macrophages pass freely through these junctions under normal conditions, and polymorphs can also pass in response to chemotaxis (page 423).

Alveolar Epithelial Cells: Type I[27]

These cells line the alveoli and exist as a thin sheet ~0.1 μm in thickness, except where expanded to contain nuclei. Like the endothelium, the flat part of the cytoplasm is devoid of organelles except for small vacuoles. Epithelial cells each cover several capillaries and are joined into a continuous sheet by tight junctions with a gap of ~1 nm.[26] These junctions may be seen as narrow lines snaking across the septa in Figure 1.7. The tightness of these junctions is crucial for prevention of the escape of large molecules, such as albumin, into the alveoli, thus preserving the oncotic pressure gradient essential for the avoidance of pulmonary oedema (see page 408). Nevertheless, these junctions permit the free passage of macrophages, and polymorphs may also pass in response to a chemotactic stimulus. Figure 1.9 shows the type I cell covered with a film of alveolar lining fluid. Type I cells are end cells and do not divide in vivo. Their position in the lung means alveolar epithelial cells are exposed to the highest concentrations of oxygen of any mammalian cell, and they are sensitive to damage from high concentrations of oxygen (Chapter 24), but recent work suggests they may have active systems for preventing oxidative stress.[28]

Alveolar Epithelial Cells: Type II

These are the stem cells from which type I cells arise. They do not function as gas exchange membranes and are rounded in shape and situated at the junction of septa. They have large nuclei and microvilli (Fig. 1.11). The cytoplasm contains characteristic striated osmiophilic organelles that contain stored surfactant (page 18). Type II cells are also involved in pulmonary defence mechanisms in that they may secrete cytokines and contribute to pulmonary inflammation. They are resistant to oxygen toxicity, tending to replace type I cells after prolonged exposure to high concentrations of oxygen.

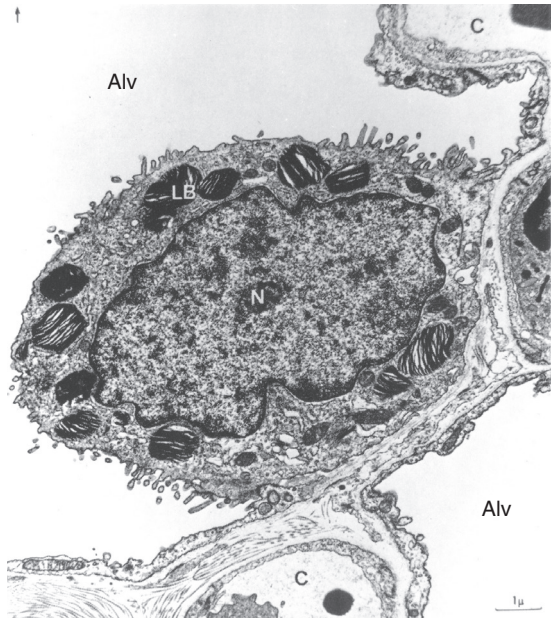

FIG. 1.11 ■ Electron micrograph of a type II alveolar epithelial cell of a dog. Note the large nucleus, the microvilli and the osmiophilic lamellar bodies thought to release surfactant. Alv, alveolus; C, capillary; LB, lamellar bodies; N, nucleus. (Reproduced from reference 29 by permission of Professor E. R. Weibel and the editors of *Physiological Reviews*.)

Alveolar Macrophages

The lung is richly endowed with these phagocytes which pass freely from the circulation, through the interstitial space and thence through the gaps between alveolar epithelial cells to lie on their surface within the alveolar lining fluid (Fig. 1.12). They can reenter the body but are remarkable for their ability to live and function outside the body. Macrophages form the major component of host defence within the alveoli, being active in combating infection and scavenging foreign bodies such as small dust particles. They contain a variety of destructive enzymes but are also capable of generating reactive oxygen species (Chapter 24). These are highly effective

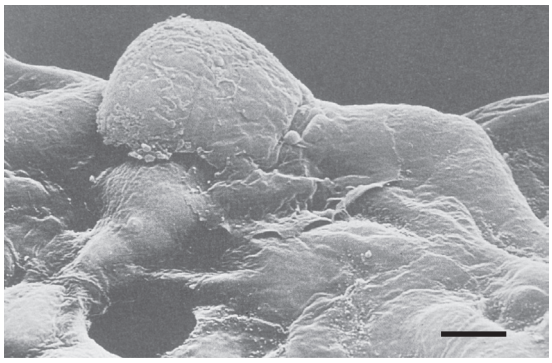

FIG. 1.12 ■ Scanning electron micrograph of an alveolar macrophage advancing to the right over epithelial type I cells. Scale bar = 3 μm. (Reproduced from reference 15 by permission of the author and the publishers; © Harvard University Press.)

bactericidal agents, but their presence in lung tissue may rebound to damage the host. Dead macrophages release the enzyme trypsin, which may cause tissue damage in patients who are deficient in the protein α_1-antitrypsin.

TABLE 1.2 **Dimensions of the Branches of the Human Pulmonary Artery**

Orders	Numbers	Mean Diameter (mm)	Cumulative Volume (ml)
17	1	30	64
16	3	15	81
15	8	8.1	85
14	20	5.8	96
13	66	3.7	108
12	203	2.1	116
11	675	1.3	122
10	2300	0.85	128
9	5900	0.53	132
8	18000	0.35	136
7	53000	0.22	138
6	160000	0.14	141
5	470000	0.086	142
4	1 400000	0.054	144
3	4 200000	0.034	145
2	13000000	0.021	146
1	300000000	0.013	151

In contrast to the airways (Table 1.1), the branching is asymmetric and not dichotomous. Singhal et al.[30] therefore grouped the vessels according to orders and not generation as in Table 1.1.

THE PULMONARY VASCULATURE

Pulmonary Arteries

Although the pulmonary circulation carries about the same flow as the systemic circulation, the arterial pressure and the vascular resistance are normally only one sixth as great. The media of the pulmonary arteries is about half as thick as in systemic arteries of corresponding size. In the larger vessels it consists mainly of elastic tissue but in the smaller vessels it is mainly muscular, the transition is in vessels of ~1-mm diameter. Pulmonary arteries lie close to the corresponding airways in connective tissue sheaths. Table 1.2 shows a scheme for consideration of the branching of the pulmonary arterial tree.[30] This may be compared with Weibel's scheme for the airways (Table 1.1).

Pulmonary Arterioles

The transition to arterioles occurs at an internal diameter of 100 μm. These vessels differ radically from their counterparts in the systemic circulation and are virtually devoid of muscular tissue. There is a thin media of elastic tissue separated from the blood by endothelium. Structurally there is no real difference between pulmonary arterioles and venules.

The normal human pulmonary circulation also contains intrapulmonary arteriovenous anastomoses involving pulmonary arterioles of 25- to 50-μm diameter.[31] These pathways are normally closed and open only when cardiac output increases,[32] for example, during exercise (page 229).[33] Their presence has clinical implications for the lung as a filtration system within the circulation (page 203).

Pulmonary Capillaries

Pulmonary capillaries tend to arise abruptly from much larger vessels, the pulmonary metarterioles. The capillaries form a dense network over the walls of one or more alveoli, and the spaces between the capillaries are similar in size to the capillaries themselves (Fig. 1.7). In the resting state, ~75% of the capillary bed is filled but the percentage is higher in the dependent parts of the lungs. Inflation of the alveoli reduces the cross-sectional area of the capillary bed and increases resistance to blood flow (Chapter 6). One capillary network is not confined to one alveolus but passes from one alveolus to another, and blood traverses a number of alveolar septa before reaching a venule. This clearly has a bearing on the efficiency of gas exchange. From the functional standpoint it is often more convenient to consider the pulmonary microcirculation rather than just the capillaries. The microcirculation is defined as the vessels that are devoid of a muscular layer and it commences

with arterioles with a diameter of 75 μm and continues through the capillary bed as far as venules with a diameter of 200 μm. Special roles of the microcirculation are considered in Chapters 11 and 28.

Pulmonary Venules and Veins

Pulmonary capillary blood is collected into venules that are structurally almost identical to the arterioles. In fact, Duke[34] obtained satisfactory gas exchange when an isolated cat lung was perfused in reverse. The pulmonary veins do not run alongside the pulmonary arteries but lie some distance away, close to the septa which separate the segments of the lung.

Bronchial Circulation[35]

The conducting airways (from trachea to the terminal bronchioles) and the accompanying blood vessels receive their nutrition from the bronchial circulation which arises from the systemic circulation. The bronchial circulation therefore provides the heat required for warming and humidification of inspired air, and cooling of the respiratory epithelium causes vasodilation and an increase in the bronchial artery blood flow. About one third of the bronchial circulation returns to the systemic venous system, the remainder draining into the pulmonary veins, constituting a form of venous admixture (page 125). The bronchial circulation also differs from the pulmonary circulation in its capacity for angiogenesis.[36] Pulmonary vessels have very limited ability to remodel themselves in response to pathological changes, whereas bronchial vessels, like other systemic arteries, can undergo prolific angiogenesis. As a result, the blood supply to most lung cancers (Chapter 29) is derived from the bronchial circulation.

Pulmonary Lymphatics

There are no lymphatics visible in the interalveolar septa, but small lymph vessels commence at the junction between alveolar and extraalveolar spaces. There is a well-developed lymphatic system around the bronchi and pulmonary vessels, capable of containing up to 500 ml of lymph, and draining towards the hilum. Down to airway generation 11 the lymphatics lay in a potential space around the air passages and vessels, separating them from the lung parenchyma. This space becomes distended with lymph in pulmonary oedema and accounts for the characteristic butterfly shadow of the chest radiograph. In the hilum of the lung, the lymphatic drainage passes through several groups of tracheobronchial lymph glands, where they receive tributaries from the superficial subpleural plexus. Most of the lymph from the left lung usually enters the thoracic duct whilst the right side drains into the right lymphatic duct. However, the pulmonary lymphatics often cross the midline and pass independently into the junction of the internal jugular and subclavian veins on the corresponding sides of the body.

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CHAPTER 1 FUNCTIONAL ANATOMY OF THE RESPIRATORY TRACT

- The **upper airway** describes the **mouth, nose and pharynx**, and is responsible for conducting air into the larynx. Mouth breathing and nasal breathing are controlled by **pharyngeal muscles**, particularly those of the tongue and soft palate. **Mouth breathing becomes obligatory** with **nasal obstruction** from common diseases and is required when hyperventilating for example, **during exercise**, to reduce respiratory resistance to high gas flows.
- **Filtration** of large inhaled particles and **humidification** of inspired gas are important roles for the upper airway and are more efficiently performed when **nasal breathing**.
- The **larynx** has many physiological roles, including **controlling the rate of expiratory airflow** by partial closure of the vocal folds, or **effort closure** in which the vocal folds close completely to allow intrathoracic pressure to be raised, for example, during a **cough**. Fine control of vocal fold position and tension is also achieved by the larynx to facilitate **phonation**, the **laryngeal component of speech**. This requires excellent coordination between the **respiratory** and **laryngeal muscles** to achieve the correct, and highly variable, **airflows through the vocal folds**.
- The term ***'conducting airways'*** describes all the air passages from the **trachea** to the **terminal bronchioles**, which is about 14 airway generations. **Airway diameter reduces** with each division from ~18 mm in the trachea to 1 mm in the bronchioles, and as the **number of airways increases** so the **cross-sectional area increases** and gas velocity decreases. **Airway integrity** is maintained by the presence of **cartilage** in the airway walls down to about the eleventh generation (small airways with diameter ≈1 mm) but beyond this airway patency is dependent on the **elasticity of the surrounding lung tissue** in which the airway is embedded.
- Conducting airways are lined with **respiratory epithelium**, which is responsible for **further humidification** of inspired gases and removal and **disposal of inhaled particles and chemicals**. The epithelium is mostly made up of ciliated cells: **pseudostratified** in the upper airway, **columnar** in large airways and **cuboidal** in bronchioles. In larger airways **submucosal glands** exist, containing secretory cells, and **goblet cells** are present throughout the airway, producing mucus. Other cells in the epithelium are **basal cells** (the stem cells for other cell types), mast cells and **nonciliated epithelial cells** (Clara cells) of uncertain function.
- A **pulmonary acinus** is the region of lung in which gas exchange occurs. The term '**acinar airways**' therefore includes all airways that have alveoli in their walls, including **respiratory bronchioles, alveolar ducts and the alveolar sacs** in which each airway terminates. The **epithelial cells** lining acinar airways gradually thin from **cuboidal** in the terminal bronchioles to become continuous with the **alveolar epithelial cells**.
- A **fibre scaffold** of collagen and elastin maintains the structure of the acinus, with interconnected **axial fibres** running along the airways, **peripheral fibres** extending from the visceral pleura into the lung tissue and **septal fibres** forming the alveolar structure itself. This basketlike structure of fibres includes many components **under tension**, such that when a small area is damaged large holes can occur as seen, for example, in emphysema.
- An adult lung contains **~400 million alveoli** with an average diameter at resting lung volume of **0.2 mm** and a total surface area of **130 m^2**. Alveoli contain **type 1 epithelial cells** over the gas exchange area, **type 2 epithelial cell**s in the corners of the alveoli which **produce surfactant** and are the **stem cells for type 1** cells, and **alveolar macrophages** responsible for removal of **inhaled particles** in the alveolus. The alveolar epithelial **and pulmonary capillary endothelial** cells are both extremely thin in the area of the alveoli where gas exchange occurs, referred to as the **'active side'** of the alveolar capillary barrier. The cell organelles and much of the interstitial space are located on the **'service side'** of the alveolus where significant gas exchange does not occur.
- **Pulmonary blood vessels** branch in a similar pattern to their corresponding airways, and, unlike their systemic counterparts, are **virtually devoid of muscular tissue**. Pulmonary **capillaries** form a **dense network** around the walls of alveoli, weaving across the septa and **bulging into the alveoli** with their active sides exposed to the alveolar gas.
- The **bronchial circulation** is separate from the pulmonary circulation, arising from the **systemic circulation** and supplying the **conducting airways**, with some of its venous drainage returning to **the right side of the systemic circulation** and some draining directly into the **pulmonary veins**.

CHAPTER 2

Elastic Forces and Lung Volumes

KEY POINTS

- Inward elastic recoil of the lung opposes outward elastic recoil of the chest wall, and the balance of these forces determines static lung volumes.
- Surface tension within the alveoli contributes significantly to lung recoil and is reduced by the presence of surfactant, though the mechanism by which this occurs is poorly understood.
- Compliance is defined as the change in lung volume per unit change in pressure gradient and may be measured for lung, thoracic cage or both.
- Various static lung volumes may be measured, and the volumes obtained are affected by a variety of physiological and pathological factors.

An isolated lung will tend to contract until eventually all the contained air is expelled. In contrast, when the thoracic cage is opened it tends to expand to a volume about 1 l greater than functional residual capacity (FRC). Thus in a relaxed subject with an open airway and no air flowing, for example, at the end of expiration or inspiration, the inward elastic recoil of the lungs is exactly balanced by the outward recoil of the thoracic cage.

The movements of the lungs are entirely passive and result from forces external to the lungs. With spontaneous breathing the external forces are the respiratory muscles, whereas artificial ventilation is usually in response to a pressure gradient developed between the airway and the environment. In each case, the pattern of response by the lung is governed by the physical impedance of the respiratory system. This impedance, or hindrance, has numerous origins, the most important of which are the following:

- Elastic resistance of lung tissue and chest wall
- Resistance from surface forces at the alveolar gas–liquid interface
- Frictional resistance to gas flow through the airways
- Frictional resistance from deformation of thoracic tissues (viscoelastic tissue resistance)
- Inertia associated with movement of gas and tissue.

The last three may be grouped together as nonelastic resistance or respiratory system resistance; they are discussed in Chapter 3. They occur while gas is flowing within the airways, and work performed in overcoming this 'frictional' resistance is dissipated as heat and lost.

The first two forms of impedance may be grouped together as 'elastic' resistance. These are measured when gas is not flowing within the lung. Work performed in overcoming elastic resistance is stored as potential energy, and elastic deformation during inspiration is the usual source of energy for expiration during both spontaneous and artificial breathing.

This chapter is concerned with the elastic resistance afforded by lungs (including the alveoli) and chest wall, which will be considered separately and then together. When the respiratory muscles are totally relaxed, these factors govern the resting end-expiratory lung volume or FRC; therefore lung volumes will also be considered in this chapter.

ELASTIC RECOIL OF THE LUNGS[1]

Lung compliance is defined as the change in lung volume per unit change in transmural pressure gradient (i.e. between the alveolus and pleural space). Compliance is usually expressed in litres (or millilitres) per kilopascal (or centimetres of water) with a normal value of 1.5 $l.kPa^{-1}$ (150 $ml.cmH_2O^{-1}$). Stiff lungs have a low compliance.

Compliance may be described as static or dynamic depending on the method of measurement (page 29). Static compliance is measured after the lungs have been held at a fixed

volume for as long as is practicable, whereas dynamic compliance is usually measured in the course of normal rhythmic breathing. Elastance is the reciprocal of compliance and is expressed in kilopascals per litre. Stiff lungs have a high elastance.

The Nature of the Forces Causing Recoil of the Lung

For many years it was thought that the recoil of the lung was due entirely to stretching of the yellow elastin fibres present in the lung parenchyma. In 1929 von Neergaard (see section on *Lung Mechanics* in online Chapter 2: The History of Respiratory Physiology) showed that a lung completely filled with and immersed in water had an elastance that was much less than the normal value obtained when the lung was filled with air. He correctly concluded that much of the 'elastic recoil' was due to surface tension acting throughout the vast air/water interface lining the alveoli.

Surface tension at an air/water interface produces forces that tend to reduce the area of the interface. Thus the gas pressure within a bubble is always higher than the surrounding gas pressure because the surface of the bubble is in a state of tension. Alveoli resemble bubbles in this respect, although the alveolar gas is connected to the exterior by the air passages. The pressure inside a bubble is higher than the surrounding pressure by an amount depending on the surface tension of the liquid and the radius of curvature of the bubble according to the Laplace equation:

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

where P is the pressure within the bubble (dyn.cm^{-2}), T is the surface tension of the liquid (dyn.cm^{-1}) and R is the radius of the bubble (cm). In coherent SI units (see Appendix A), the appropriate units would be pressure in pascals (Pa), surface tension in newtons/metre (N.m^{-1}) and radius in metres (m).

Figure 2.1, *A*, left, shows a typical alveolus with a radius 0.1 mm. Assuming that the alveolar lining fluid has a normal surface tension of 20 mN.m^{-1} (20 dyn.cm^{-1}), the pressure within the alveolus will be 0.4 kPa (4 cmH_2O), which is rather less than the normal transmural pressure at FRC. If the alveolar lining fluid had the same surface tension as water (72 mN.m^{-1}), the lungs would be very stiff.

The alveolus in Figure 2.1, *A*, right, has a radius of only 0.05 mm and the Laplace equation indicates that, if the surface tension of the alveolus is the same, its pressure should be double the pressure in the left-hand alveolus. Thus gas would tend to flow from smaller alveoli into larger alveoli and the lung would be unstable which, of course, is not true. Similarly, the retractive forces of the alveolar lining fluid would increase at low lung volumes and decrease at high lung volumes, which is exactly the reverse of what is observed. These paradoxes were clear to von Neergaard and he concluded that the surface tension of the alveolar lining fluid must be considerably less than would be expected from the properties of simple liquids and, furthermore, that its value must be variable. Observations 30 years later confirmed this when alveolar extracts were shown to have a surface tension much lower than water and which varied in proportion to the area of the interface.[2] Figure 2.1, *B*, shows an experiment in which a floating bar is moved in a trough containing an alveolar extract. As the bar is moved to the right, the surface film is concentrated and the surface tension changes as shown in the graph on the right of the figure. During expansion, the surface tension increases to 40 mN.m^{-1}, a value which is close to that of plasma but, during contraction, the surface tension falls to 19 mN.m^{-1}, a lower value than any other body fluid. The course of the relationship between pressure and area is different during expansion and contraction, and a loop is described.

The consequences of these changes are important. In contrast to a bubble of soap solution, the pressure within an alveolus tends to decrease as the radius of curvature is decreased. This is illustrated in Figure 2.1, *C*, in which the right-hand alveolus has a smaller diameter and a much lower surface tension than the left-hand alveolus. Gas tends to flow from the larger to the smaller alveolus and stability is maintained.

The Alveolar Surfactant

The low surface tension of the alveolar lining fluid and its dependence on alveolar radius are due to the presence of a surface-active material known as surfactant. Approximately 90% of surfactant consists of lipids, and the remainder is proteins and small amounts of carbohydrate. Most of the lipid is phospholipid, of which 70% to 80% is dipalmitoyl phosphatidyl choline (DPPC), the main constituent responsible for the effect on surface tension. The fatty acids are hydrophobic and generally straight, lying parallel to each other and projecting into the gas phase. The other end of the molecule is

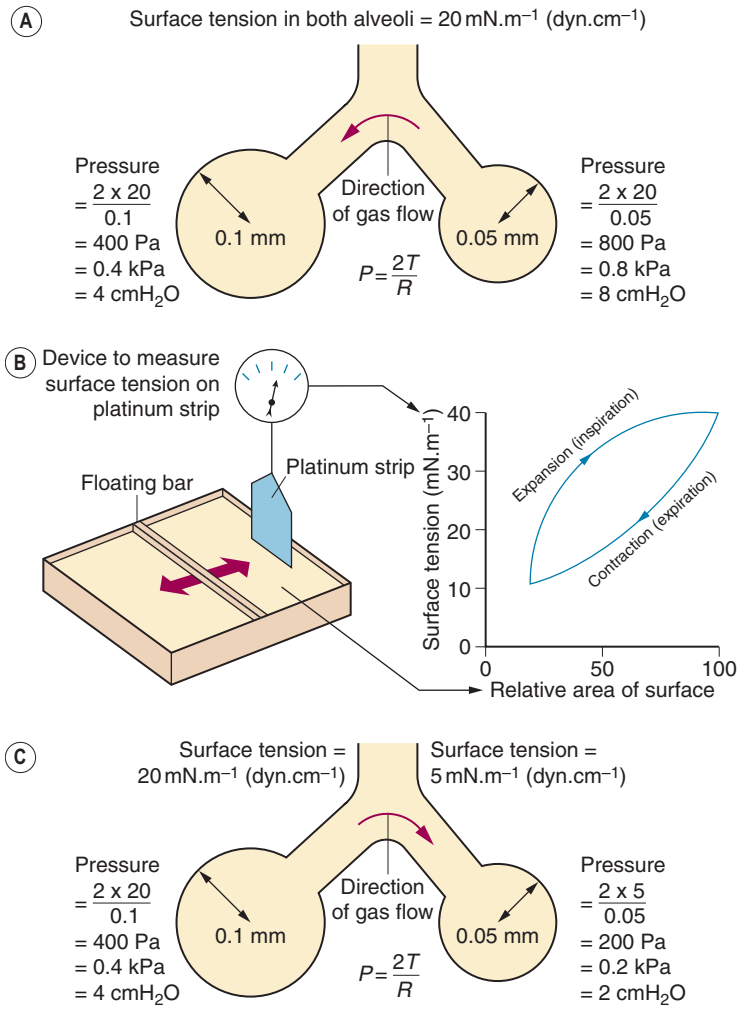

FIG. 2.1 ■ Surface tension and alveolar transmural pressure. **(A)** Pressure relations in two alveoli of different size but with the same surface tension of their lining fluids. **(B)** The changes in surface tension in relation to the area of the alveolar lining film. **(C)** Pressure relations of two alveoli of different size when allowance is made for the probable changes in surface tension.

hydrophilic and lies within the alveolar lining fluid. The molecule is thus confined to the surface where, being detergents, they lower surface tension in proportion to the concentration at the interface.

Approximately 2% of surfactant by weight consists of surfactant proteins (SPs), of which there are four types labelled A to D.[3,4] SP-B and SP-C are small proteins vital to the stabilization of the surfactant monolayer (see later); a congenital lack of SP-B results in severe and progressive respiratory failure,[4,5] and genetic abnormalities of SP-C lead to pulmonary fibrosis in later life.[6] SP-A, and to a lesser extent SP-D, are involved in the control of surfactant release and possibly in preventing pulmonary infection (see later).[7]

Synthesis of Surfactant

Surfactant is both formed in and liberated from the alveolar epithelial type II cell (page 13). The lamellar bodies (Fig. 1.11) contain stored surfactant that is released into the alveolus by exocytosis in response to high volume lung inflation, increased ventilation rate or endocrine stimulation. After release surfactant initially forms areas of a lattice structure termed tubular myelin, which is then reorganized into monolayered or multilayered surface films. This conversion into the functionally active form of surfactant is critically dependent on SP-B and SP-C (see later).[4,6] The alveolar half-life of surfactant is 15 to 30 h with most of its components recycled by type II alveolar cells. SP-A is intimately involved in

controlling the surfactant present in the alveolus with type II alveolar cells having SP-A surface receptors, the stimulation of which exerts negative feedback on surfactant secretion and increases reuptake of surfactant components into the cell.

Action of Surfactant

To maintain the stability of alveoli as shown in Figure 2.1, surfactant must alter the surface tension in the alveoli as their size varies with inspiration and expiration. A simple explanation of how this occurs is that during expiration, as the surface area of the alveolus diminishes, the surfactant molecules are packed more densely and so exert a greater effect on the surface tension, which then decreases as shown in Figure 2.1, *B*. In reality, the situation is considerably more complex, and at present poorly elucidated.[4] The classical explanation, referred to as the 'squeeze out' hypothesis, is that as a surfactant monolayer is compressed, the less stable phospholipids are squeezed out of the layer, increasing the amount of stable DPPC molecules which have the greatest effect in reducing surface tension.[8] Surfactant phospholipid is also known to exist in vivo in both monolayer and multilayer forms,[3] and it is possible that in some areas of the alveoli the surfactant layer alternates between these two forms as alveolar size changes during the respiratory cycle. This aspect of surfactant function is entirely dependent on the presence of SP-B, a small hydrophobic protein, which can be incorporated into a phospholipid monolayer, and SP-C, a larger protein with a hydrophobic central portion allowing it to span a lipid bilayer.[4] When alveolar size reduces and the surface film is compressed, SP-B molecules may be squeezed out of the lipid layer changing its surface properties, whereas SP-C may serve to stabilize bilayers of lipid to act as a reservoir from which the surface film reforms when alveolar size increases.

Other Effects of Surfactant

Pulmonary transudation is also affected by surface forces. Surface tension causes the pressure within the alveolar lining fluid to be less than the alveolar pressure. Because the pulmonary capillary pressure in most of the lung is greater than the alveolar pressure (page 408), both factors encourage transudation, a tendency checked by the oncotic pressure of the plasma proteins. Thus the surfactant, by reducing surface forces, diminishes one component of the pressure gradient and helps to prevent transudation.

Surfactant also plays an important part in the immunology of the lung.[9,10] The lipid component of surfactant has antioxidant activity and may attenuate lung damage from a variety of causes, suppressing some groups of lymphocytes, theoretically protecting the lungs from autoimmune damage. In vitro studies have shown that SP-A or SP-D can bind to a wide range of pulmonary pathogens including viruses, bacteria, fungi, *Pneumocystis jirovecii*, and *Mycobacterium tuberculosis*. Polymorphisms of the surfactant genes are associated with the severity of some respiratory diseases, for example, the likelihood of developing severe pulmonary manifestations of an influenza infection is influenced by a single nucleotide polymorphism of SP-B.[11] Acting via specific surface receptors, both SP-A and SP-D activate alveolar neutrophils and macrophages and enhance the phagocytic actions of the latter during lung inflammation.[10]

Alternative Models to Explain Lung Recoil

Treating surfactant-lined alveoli as bubbles that obey Laplace's law has aided the understanding of lung recoil in health and disease for many decades (see section on *Lung Mechanics* in online Chapter 2: The History of Respiratory Physiology). This 'bubble model' of alveolar stability is not universally accepted,[12] and there is evidence that the real situation is more complex. Arguments against the bubble model include the following:

- In theory, differing surface tensions in adjacent alveoli cannot occur if the liquid lining the alveoli is connected by a continuous liquid layer.
- When surfactant layers are compressed at 37°C multilayered 'rafts' of dry surfactant form, though inclusion of surfactant proteins reduces this physicochemical change.
- Alveoli are not shaped like perfect spheres with a single entrance point; they are variable polyhedrons with convex bulges in their walls where pulmonary capillaries bulge into them (Fig. 1.7).

Two quite different alternative models have been proposed:

Morphological model. Hills' model proposes that the surfactant lining alveoli results in a 'discontinuous' liquid lining.[13,14] Based on knowledge of the physical chemistry of surfactants, this model shows that surfactant phospholipids are adsorbed directly onto the epithelial cell surface, forming multilayered rafts of surfactant (Fig. 2.2). These rafts cause patches of the surface to become less wettable, and these areas are

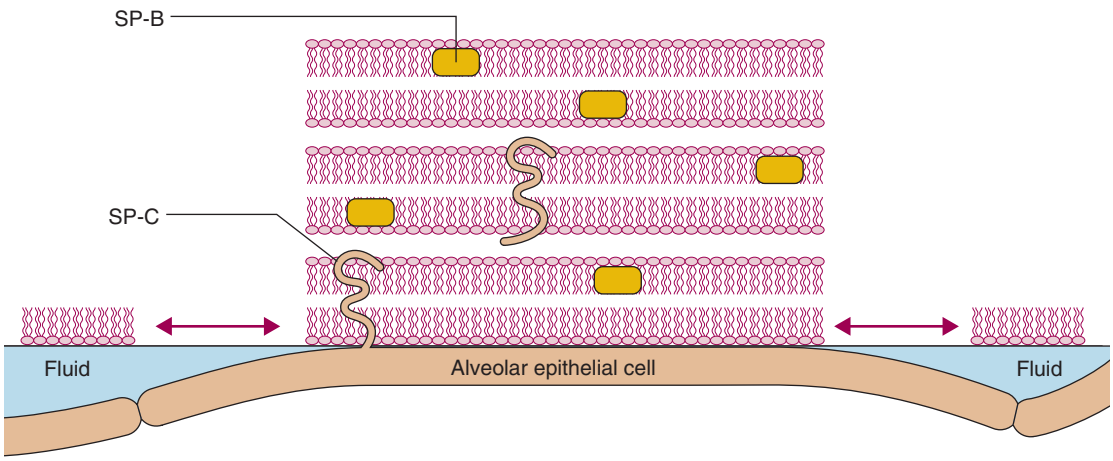

FIG. 2.2 ■ Morphological model of alveolar surfactant. Multilayered, less wettable, rafts of surfactant are interspersed with fluid pools. Surfactant proteins lie within (SP-B) or across (SP-C) the lipid bilayers, facilitating the formation and dispersion of the rafts with each breath to modify the surface forces within the alveolus. (Reproduced with permission from Webster NR, Galley HF. Anaesthesia Science. Oxford: Blackwell Publishing, 2006.)

interspersed with fluid pools. Surface forces generated by the interaction between the 'dry' areas of surfactant and the areas of liquid are theoretically large enough to maintain alveolar stability. The rafts of surfactant may be many layers thick, and are believed to form and disperse with each breath; their function is almost certainly dependent on both SP-B and SP-C.

Foam model. Scarpelli developed different techniques for preparing lung tissue for microscopy.[15] By maintaining tissue in a more natural state than previous studies, including keeping lung volume close to normal, he described a 'new anatomy' for alveoli. Scarpelli's findings seem to show that in vivo alveoli have bubble films across their entrances, with similar lipid bilayer films also existing across alveolar ducts and respiratory bronchioles (Fig. 2.3). In this model, each acinus may be considered as a series of interconnected, but closed, bubbles forming a stable 'foam.' The bubble films are estimated to be less than 7-nm thick,[16] offering little resistance to gas diffusion, the normal mechanism by which gas movement occurs in a single pulmonary acinus (page 9).

More research is clearly needed to either confirm or refute these models. It would therefore be premature to consign the well-established bubble model of alveolar recoil to the history books, but physiologists should be aware that cracks have begun to appear in the longstanding physiological concept.

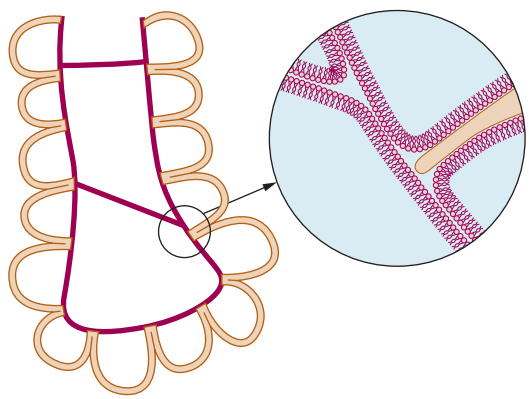

FIG. 2.3 ■ Scarpelli's foam model of alveolar structure.[15] Surfactant (red) lines the alveoli and forms films that span both the alveolar openings and the alveolar ducts. **Inset,** detail of the surfactant layer showing connection between phospholipid monolayer and bilayer (not to scale).

Transmural Pressure Gradient and Intrathoracic Pressure

The transmural pressure gradient is the difference between intrathoracic (or 'intrapleural') and alveolar pressure. The pressure within an alveolus is always greater than the pressure in the surrounding interstitial tissue except when the volume has been reduced to zero. By increasing lung volume, the transmural pressure gradient steadily increases, as shown for the whole lung in Figure 2.4. If an appreciable pneumothorax is present, the pressure gradient from alveolus to pleural cavity provides a measure of the overall

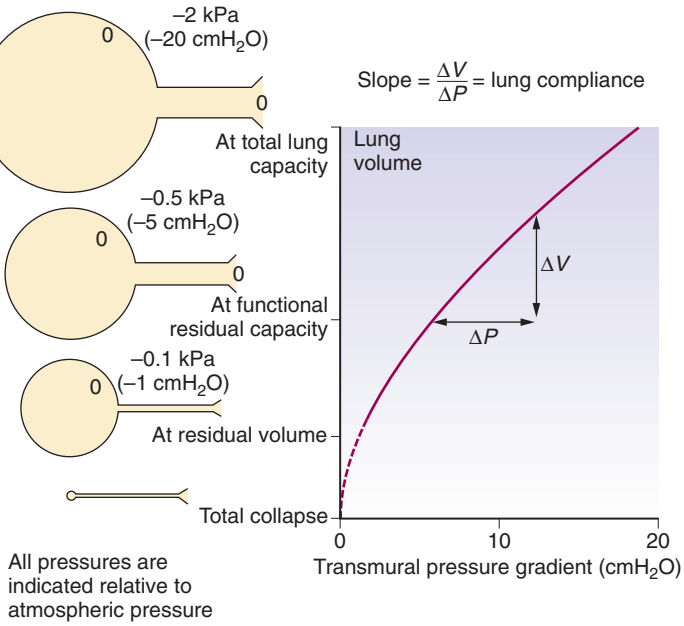

FIG. 2.4 ■ Relationship between lung volume and the difference in pressure between the alveoli and the intrathoracic space (transmural pressure gradient). The relationship is almost linear over the normal tidal volume range. The calibre of small air passages decreases in parallel with alveolar volume. Airways begin to close at the closing capacity and there is widespread airway closure at residual volume. Values in the diagram relate to the upright position and to *decreasing* pressure. The opening pressure of a closed alveolus is not shown.

transmural pressure gradient. Otherwise, the oesophageal pressure may be used to indicate the pleural pressure, but there are conceptual and technical difficulties. The technical difficulties are considered at the end of this chapter whereas some of the conceptual difficulties are indicated in Figure 2.5.

The alveoli in the upper part of the lung have a larger volume than those in the dependent part, except at total lung capacity. The greater degree of expansion of the alveoli in the upper part results in a greater transmural pressure gradient, which decreases steadily down the lung at approximately 0.1 kPa (or 1 cmH_2O) per 3 cm of vertical height; such a difference is indicated in Figure 2.5, *A*. Because the pleural cavity is normally empty, it is not strictly correct to speak of an intrapleural pressure; furthermore, it would not be constant throughout the pleural 'cavity.' One should think rather of the relationship shown in Figure 2.4 as applying to various horizontal strata of the lung, each with its own volume and therefore its own transmural pressure gradient on which its own intrapleural pressure would depend. The transmural pressure gradient has an important influence on many aspects of pulmonary function, so its horizontal stratification confers a regional difference on many features of pulmonary function, including airway closure and ventilation/perfusion ratios, and therefore gas exchange. These matters are considered in detail in Chapters 3 and 7.

At first sight it might be thought that the subatmospheric intrapleural pressure would result in the accumulation of gas evolved from solution in blood and tissues. In fact the total of the partial pressures of gases dissolved in blood, and therefore tissues, is always less than 1 atm (see Table 24.2), and this factor keeps the pleural cavity free of gas.

Time Dependence of Pulmonary Elastic Behaviour

If an excised lung is rapidly inflated and then held at the new volume, the inflation pressure falls exponentially from its initial value to reach a lower level attained after a few seconds. This also occurs in the intact subject and is readily observed during an inspiratory pause in a patient receiving artificial ventilation (page 30). It is broadly true to say that the volume change divided by the initial change in transmural pressure gradient corresponds to the dynamic compliance, whereas the volume change divided by the ultimate change in transmural pressure gradient (i.e. measured after it has become steady) corresponds to the static compliance. Static

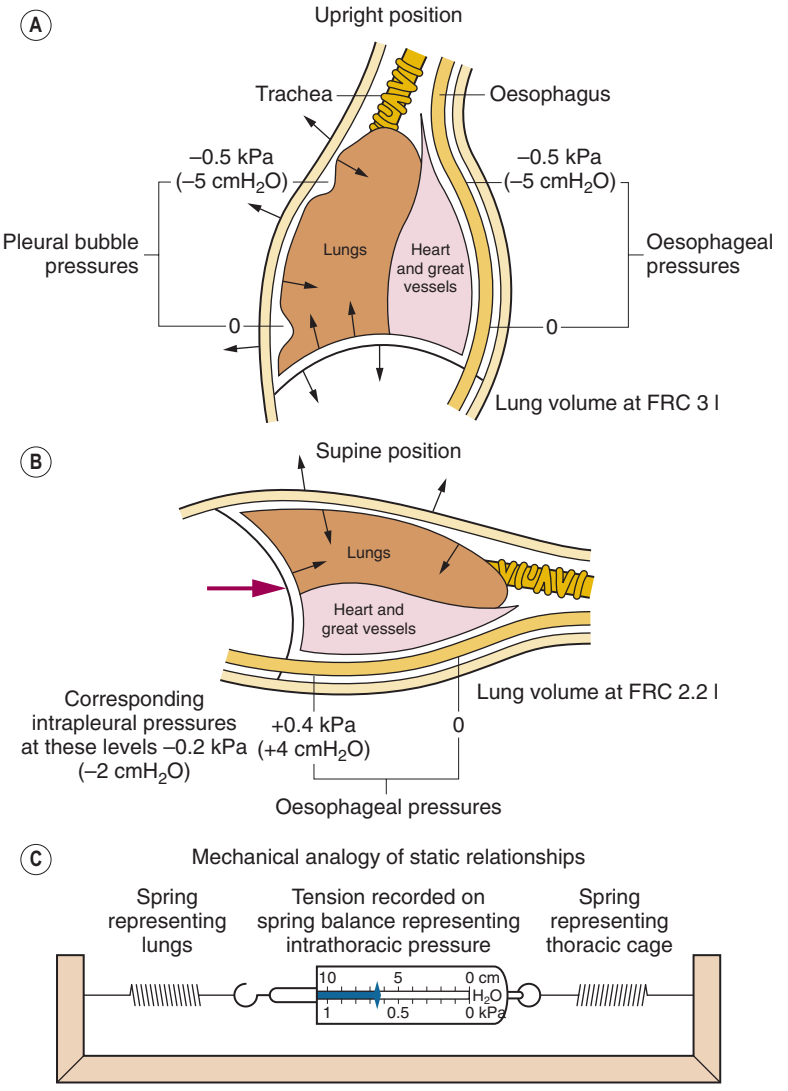

FIG. 2.5 ■ Intrathoracic pressures: static relationships in the resting end-expiratory position. The lung volume corresponds to the FRC. **(A)** and **(B)** Indicate the pressure relative to ambient (atmospheric). Arrows show the direction of elastic forces. The heavy arrow in **(B)** indicates displacement by the abdominal viscera. **(C)** The tension in the two springs is the same and will be indicated on the spring balance. In the supine position: *1,* the FRC is reduced; *2,* the intrathoracic pressure is raised; *3,* the weight of the heart raises the oesophageal pressure above the intrapleural pressure.

compliance will thus be greater than the dynamic compliance by an amount determined by the degree of time dependence in the elastic behaviour of a particular lung. The respiratory frequency has been shown to influence dynamic pulmonary compliance in the normal subject, but frequency dependence is much more pronounced in the presence of pulmonary disease.

Hysteresis

If the lungs are slowly inflated and then slowly deflated, the pressure/volume curve for static points during inflation differs from that obtained during deflation. The two curves form a loop, which becomes progressively broader as the tidal volume is increased (Fig. 2.6). Expressed in words, the loop in Figure 2.6 means that rather more than the expected pressure is required during inflation and rather less than the expected recoil pressure is available during deflation. This resembles the behaviour of perished rubber or polyvinyl chloride, both of which are reluctant to accept deformation under stress but, once deformed, are again reluctant to assume their original shape. This phenomenon is present to a

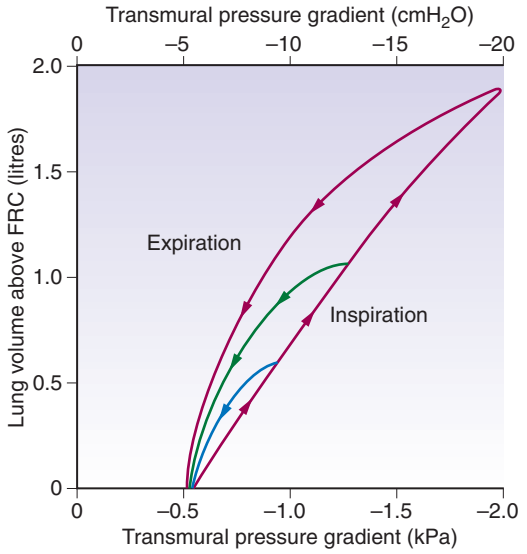

FIG. 2.6 ■ Static plot of lung volume against transmural pressure gradient (intraoesophageal pressure relative to atmospheric at zero air flow). Note that inspiratory and expiratory curves form a loop that gets wider the greater the tidal volume. These loops are typical of elastic hysteresis. For a particular lung volume, the elastic recoil of the lung during expiration is always less than the distending transmural pressure gradient required during inspiration at the same lung volume.

greater or lesser extent in all elastic bodies and is known as elastic hysteresis.

Causes of Time Dependence of Pulmonary Elastic Behaviour

There are many possible explanations of the time dependence of pulmonary elastic behaviour, the relative importance of which may vary in different circumstances.

Changes in surfactant activity. It has been explained previously that the surface tension of the alveolar lining fluid is greater at larger lung volume and also during inspiration than at the same lung volume during expiration (Fig. 2.1, *B*). This is probably the most important cause of the observed hysteresis in the intact lung (Fig. 2.6).

Stress relaxation. If a spring is pulled out to a fixed increase in its length, the resultant tension is maximal at first and then declines exponentially to a constant value. This is an inherent property of elastic bodies, known as stress relaxation. Thoracic tissues display stress relaxation and these 'viscoelastic' properties contribute significantly to the difference between static and dynamic compliance as well as forming a component of pulmonary resistance (page 36). The crinkled structure of collagen in the lung (Fig. 1.10) is likely to favour stress relaxation and excised strips of human lung show stress relaxation when stretched.

Redistribution of gas. In a lung consisting of functional units with identical time constants* of inflation, the distribution of gas should be independent of the rate of inflation, and there should be no redistribution when the lungs are held inflated. However, if different parts of the lungs have different time constants, the distribution of inspired gas will be dependent on the rate of inflation and redistribution (pendelluft) will occur when inflation is held. This problem is discussed in detail on page 111 but for the time being we can distinguish 'fast' and 'slow' alveoli (the term *alveoli* here refers to functional units rather than the anatomical entity). The fast alveolus has a low airway resistance and/or low compliance (or both) whereas the slow alveolus has a high airway resistance and/or a high compliance (Fig. 2.7, *B*). These properties give the fast alveolus a shorter time constant and are preferentially filled during a short inflation. This preferential filling of alveoli with low compliance gives an overall higher pulmonary transmural pressure gradient. A slow or sustained inflation permits increased distribution of gas to slow alveoli and tends to distribute gas in accord with the compliance of the different functional units. There should then be a lower overall transmural pressure and no redistribution of gas when inflation is held. The extreme difference between fast and slow alveoli shown in Figure 2.7, *B*, applies to diseased lungs and no such difference exists in normal lungs. Gas redistribution is therefore unlikely to be a major factor in healthy subjects, but it can be important in patients with airways disease.

Recruitment of alveoli. Below a certain lung volume, some alveoli tend to close and only reopen at a greater lung volume and in response to a higher transmural pressure gradient than that at which they closed. Despite this need for higher

*Time constants are used to describe the exponential filling and emptying of a lung unit. One time constant is the time taken to achieve 63% of maximal inflation or deflation of the lung unit. See Appendix E for details.

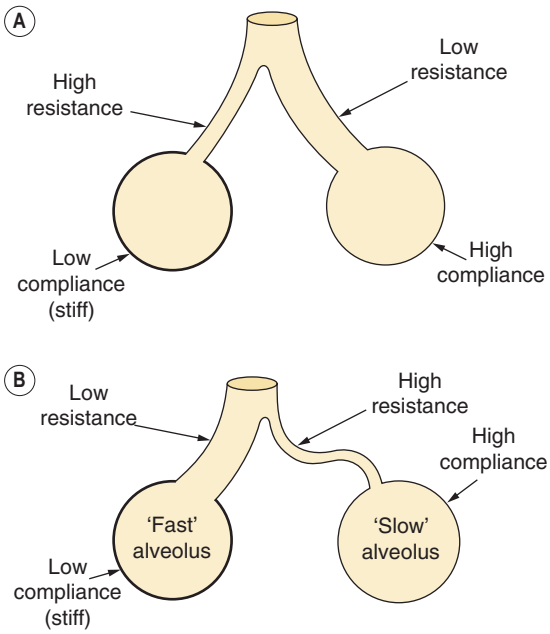

FIG. 2.7 ■ Schematic diagrams of alveoli to illustrate conditions under which static and dynamic compliance may differ. **(A)** Represents a theoretically ideal state in which there is a reciprocal relationship between resistance and compliance resulting in gas flow being preferentially delivered to the most compliant regions, regardless of the state of inflation. Static and dynamic compliance are equal. This situation is probably never realized even in the normal subject. **(B)** Illustrates a state that is typical of many patients with respiratory disease. The alveoli can conveniently be divided into fast and slow groups. The direct relationship between compliance and resistance results in inspired gas preferentially delivered to the stiff alveoli if the rate of inflation is rapid. An end-inspiratory pause then permits redistribution from the fast alveoli to the slow alveoli.

pressure to open lung units, recruitment of alveoli is a plausible explanation for the time-dependent phenomena described earlier, and there is now some evidence that this does occur in healthy lungs at FRC.

Factors Affecting Lung Compliance

Lung volume. It is important to remember that compliance is related to lung volume. This factor may be excluded by relating compliance to FRC to yield the specific compliance (i.e. compliance/FRC), which in humans is almost constant for both sexes and all ages down to neonatal. The relationship between compliance and lung volume is true not only within an individual lung but also between species. Larger animal species have thicker alveolar septa containing increased amounts of collagen and elastin resulting in larger alveolar diameters, so reducing the pressure needed to expand them. An elephant therefore has larger alveoli and higher compliance than a mouse.

Posture. Lung volume, and therefore compliance, changes with posture (page 27). There are, however, problems in the measurement of intrapleural pressure in the supine position, and when this is taken into account it seems unlikely that changes of posture have any significant effect on the specific compliance.

Pulmonary blood volume. The pulmonary blood vessels probably make an appreciable contribution to the stiffness of the lung. Pulmonary venous congestion from whatever cause is associated with reduced compliance.

Age. There is a small increase in lung compliance with increasing age, believed to be caused by changes to the structure of lung collagen and elastin rather than changes in the amount or proportion of the two molecules in the lung connective tissue.[17,18] The small magnitude of these age-related changes is in accord with the concept of lung 'elasticity' being largely determined by surface forces.

Bronchial smooth muscle tone. Animal studies[19] have shown that an infusion of methacholine sufficient to result in a doubling of airway resistance decreases dynamic compliance by 50%. The airways might contribute to overall compliance or, alternatively, bronchoconstriction could enhance time dependence and reduce dynamic, but perhaps not static, compliance (Fig. 2.7). This interdependence between small airways and their surrounding alveoli also affects airway resistance (page 37).

Disease. Important changes in lung pressure–volume relationships are found in some lung diseases, and these are described in Part 3.

ELASTIC RECOIL OF THE THORACIC CAGE

The thoracic cage comprises the ribcage and the diaphragm. Each is a muscular structure and can be considered as an elastic structure only when the muscles are relaxed, which is not easy to achieve except under the conditions of paralysis. Relaxation curves have been prepared relating

pressure and volumes in the supposedly relaxed subject, but it is now doubted whether total relaxation was ever achieved. For example, in the supine position the diaphragm is not fully relaxed at the end of expiration but maintains a resting tone to prevent the abdominal contents from pushing the diaphragm cephalad.

Compliance of the thoracic cage is defined as change in lung volume per unit change in the pressure gradient between atmosphere and the intrapleural space. The units are the same as for pulmonary compliance. The measurement is seldom made but the value is of the order of 2 $l.kPa^{-1}$ (200 $ml.cmH_2O^{-1}$).

Factors Influencing Compliance of the Thoracic Cage

Anatomical factors include the ribs and the state of ossification of the costal cartilages, which explains the progressive reduction in chest wall compliance with increasing age.[17] Obesity and even pathological skin conditions may also have an appreciable effect. In particular, scarring of the skin overlying the front of the chest, for example, from burns, may impair breathing.

In terms of compliance, a relaxed diaphragm simply transmits pressure from the abdomen that may be increased in obesity and abdominal distension. Posture clearly has a major effect and this is considered below in relation to FRC. Compared with the supine position, thoracic cage compliance is 30% greater in the seated subject and the total static compliance of the respiratory system is reduced by 60% in the prone position because of the diminished elasticity of the ribcage and diaphragm when prone.

PRESSURE/VOLUME RELATIONSHIPS OF THE LUNG PLUS THORACIC CAGE

Compliance is analogous to electrical capacitance, and in the respiratory system the compliance of lungs and thoracic cage are in series. Therefore the total compliance of the system obeys the same relationship as that for capacitances in series, in which reciprocals are added to obtain the reciprocal of the total value, thus

$$\frac{1}{\text{total compliance}} = \frac{1}{\text{lung compliance}} + \frac{1}{\text{thoracic cage compliance}}$$

typical static values ($l.kPa^{-1}$) for the supine paralysed patient are

$$\frac{1}{0.85} = \frac{1}{1.5} + \frac{1}{2}.$$

Instead of compliance, we may consider its reciprocal, elastance. The relationship is then much simpler:

$$\text{Total elastance} = \text{lung elastance} + \text{thoracic cage elastance}$$

corresponding values ($kPa.l^{-1}$) are then

$$1.17 = 0.67 + 0.5$$

Relationship between Alveolar, Intrathoracic and Ambient Pressures

At all times the alveolar/ambient pressure gradient is the sum of the alveolar/intrathoracic (or transmural) and intrathoracic/ambient pressure gradients. This relationship is independent of whether the patient is breathing spontaneously or being ventilated by intermittent positive pressure. Actual values depend on compliances, lung volume and posture and typical values are shown for the upright, conscious relaxed subject in Figure 2.8. The values in the illustration are static and relate to conditions when no gas is flowing.

STATIC LUNG VOLUMES

Certain lung volumes, particularly the FRC, are determined by elastic forces. This is therefore a convenient point at which to consider the various lung volumes and their subdivision (Fig. 2.9).

Total lung capacity (TLC). This is the volume of gas in the lungs at the end of a maximal inspiration. TLC is achieved when the maximal force generated by the inspiratory muscles is balanced by the forces opposing expansion. It is rather surprising that expiratory muscles are also contracting strongly at the end of a maximal inspiration.

Residual volume (RV). This is the volume remaining after a maximal expiration. In the young, RV is governed by the balance between the maximal force generated by expiratory muscles and the elastic forces opposing reduction of lung volume.

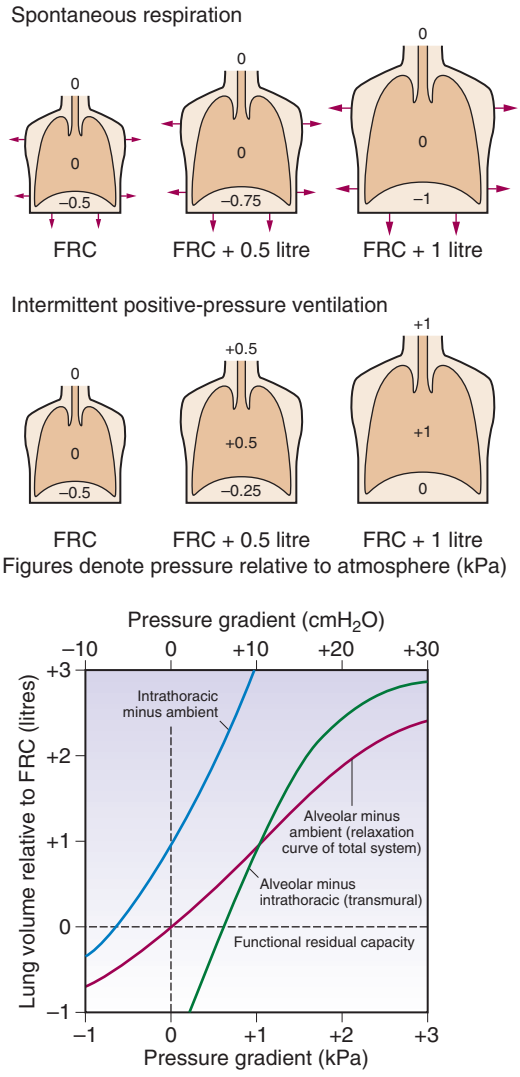

FIG. 2.8 ■ Static pressure/volume relations for the intact thorax for the conscious subject in the upright position. The transmural pressure gradient bears the same relationship to lung volume during both intermittent positive pressure ventilation and spontaneous breathing. The intrathoracic-to-ambient pressure difference, however, differs in the two types of ventilation due to muscle action during spontaneous respiration. At all times: alveolar/ambient pressure difference = alveolar/intrathoracic pressure difference + intrathoracic/ambient pressure difference (due attention being paid to the sign of the pressure difference). FRC, functional residual capacity.

However, in older subjects closure of small airways may prevent further expiration.

FRC. This is the lung volume at the end of a normal expiration.

Within the framework of TLC, RV and FRC, the other capacities and volumes shown in Figure 2.9 are self-explanatory. A 'capacity' usually refers to a measurement comprised of more than one 'volume.'

Factors Affecting Static Lung Volumes[20]

So many factors affect the FRC and other lung volumes that they require a special section of this chapter.

Body size. FRC and other lung volumes are linearly related to subject height.

Sex. For the same body height, females have a FRC about 10% less than males and a smaller forced vital capacity (FVC), the latter resulting from males having less body fat and a more muscular chest.

Age. FVC, FRC and RV all increase with age, but at different rates, with corresponding changes in the other lung volumes as shown in Figure 2.10. On average, FRC increases by around 16 ml per year.

Posture. Figure 2.11, *A*, shows the changes in lung volumes between the upright (seated) and supine positions, showing a significantly reduced FRC when supine. The changes are caused by the increased pressure of the abdominal contents on the diaphragm in the supine position, displacing it in a cephalad direction and reducing thoracic volume. This is further demonstrated in Figure 2.12 and Table 2.1 showing the influence of different degrees of body tilting and other body positions on FRC. Values of FRC in these figures and Table 2.1 are typical for a subject of 1.70 m height, and reported mean differences between supine and upright positions ranging from 500 to 1000 ml.

Ethnic group. Values for lung volumes vary between the different principal ethnic groups in the world even after age and stature have been taken into account. Causes of these differences include geographic location, diet and levels of activity in childhood, all of which can influence lung development. Increasing global migration and interbreeding between ethnic groups is now causing difficulties with interpretation of ethnicity as a component of normal lung volumes.[20]

Obesity. With the exception of tidal volume, obesity causes a reduction in all static lung volumes, particularly expiratory reserve volume and so FRC (Fig. 2.11, *B*).[21] The effects of obesity are worse in the supine compared with seated position, and in both positions arise from increased intraabdominal pressure displacing the diaphragm into the chest cavity. In obese and non-obese subjects static compliance is similar when measured at normal lung

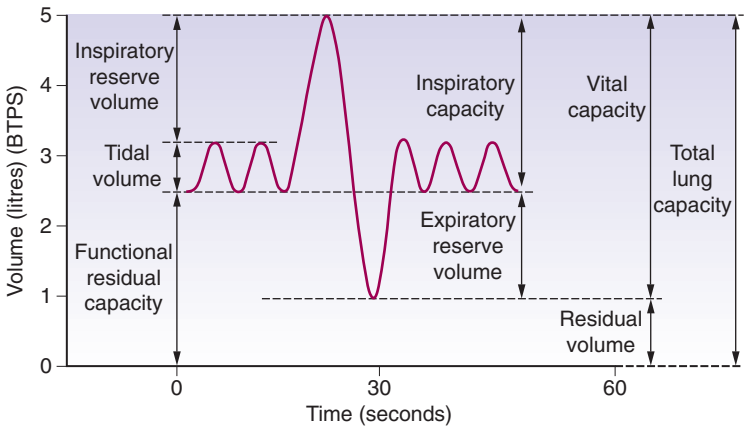

FIG. 2.9 ■ Static lung volumes of Dr. Nunn in 1990. The 'spirometer curve' indicates the lung volumes that can be measured by simple spirometry. These are tidal volume, inspiratory reserve volume, inspiratory capacity, expiratory reserve volume and vital capacity. The residual volume, total lung capacity and functional residual capacity cannot be measured by observation of a spirometer without further elaboration of methods. BTPS, body temperature and pressure, saturated.

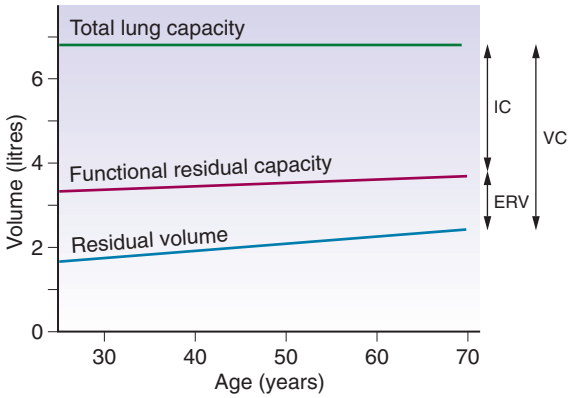

FIG. 2.10 ■ Changes in static lung volumes with age. The largest change is in residual volume, the increase in which reduces both expiratory reserve volume (ERV) and vital capacity (VC) while inspiratory capacity (IC) remains mostly unchanged. (After reference 17.)

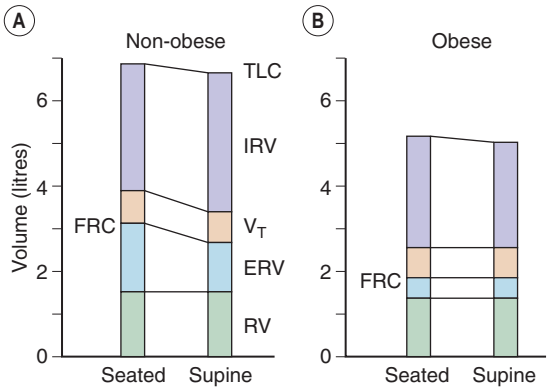

FIG. 2.11 ■ Effects of position and obesity on static lung volumes. **(A)** Nonobese subjects with a mean body mass index (BMI) of 23.2. Note the reduction in expiratory reserve volume (ERV) and so functional residual capacity (FRC) when supine due to the weight of the abdominal contents displacing the diaphragm in a cephalad direction. **(B)** Severely obese subjects with a mean BMI of 46.8, in whom intraabdominal pressure is increased irrespective of body position, causing an even greater reduction in ERV and FRC. V_T, tidal volume; RV, residual volume, IRV, inspiratory reserve volume; TLC, total lung capacity. (Reproduced from reference 21 with permission from BMJ Publishing Group Ltd.)

volume, but is reduced at high lung volume in the obese. As a result of their low FRC obese subjects are therefore breathing at a less favourable part of their compliance curve, which contributes to an increased work of breathing (page 82).

All of the factors described so far must be taken into account when attempting to ascertain 'normal' values for lung volumes in an individual subject. For example, a predicted normal value for FRC in an individual Caucasian male aged between 25 to 65 years and in an upright posture may be calculated from[20]

$$\text{FRC} = (5.95 \times \text{height}) + (0.019 \times \text{age}) - (0.086 \times \text{BMI}) - 5.3$$

where FRC is in litres, height in meters, age in years, and body mass index (BMI) in $kg.m^{-2}$. This type of calculation is routinely performed when measuring lung volumes, and the ideal way of reporting the results is as a percentage of predicted i.e. actual measured volume divided by calculated normal for the individual. The diagnosis of many respiratory diseases is dependent on this percentage result (Chapter 27);

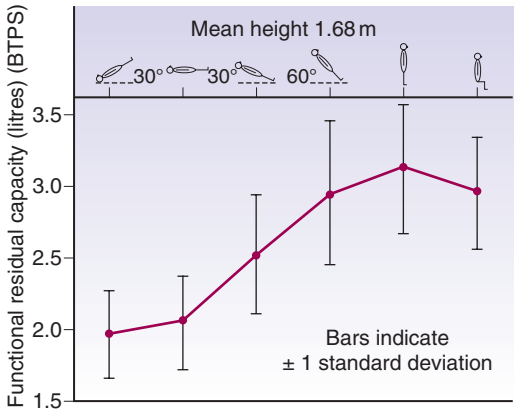

FIG. 2.12 ■ Studies by Dr. Nunn and his co-workers of the functional residual capacity in various body positions. BTPS, body temperature and pressure, saturated.

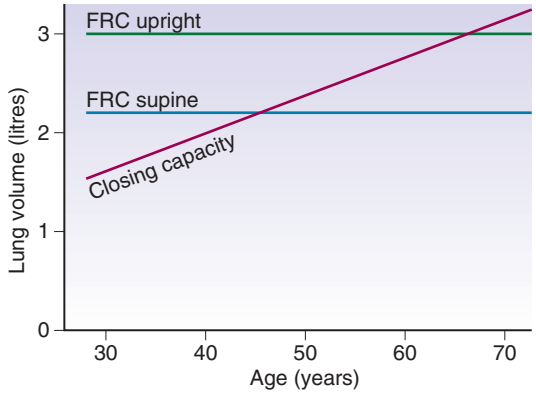

FIG. 2.13 ■ Functional residual capacity (FRC) and closing capacity as a function of age. (Data from reference 24.)

TABLE 2.1 **Effect of Posture on Some Aspects of Respiratory Function**[22]

Position	FRC (l) (BTPS)	Ribcage Breathing* (%)	Forced Expiratory Volume In 1 s (l) (BTPS)
Sitting	2.91	69.7	3.79
Supine	2.10	32.3	3.70
Supine (arms up)	2.36	33.0	3.27
Prone	2.45	32.6	3.49
Lateral	2.44	36.5	3.67

Data for 13 healthy males aged 24 to 64.
*Proportion of breathing accounted for by movement of the ribcage.
BTPS, body temperature and pressure, saturated.

therefore agreement on the correct formula to use is critical.[23] Extrapolating outside of the population used to develop the predictive equation is a real problem, for example, using an equation based on readings taken from Caucasian subjects aged 25 to 70 years to predict a normal value for an non-Caucasian subject aged 75 will give a misleading result. Furthermore, differences in the predictive equations used can lead to a large variation in the population prevalence of common respiratory diseases which depend on lung volumes for their diagnosis.[23]

FRC in Relation to Closing Capacity

In Chapter 3 it is explained how reduction in lung volume below a certain level results in airway closure with relative or total underventilation in the dependent parts of the lung. The lung volume below which this effect becomes apparent is known as the closing capacity (CC). With increasing age, CC rises until it equals FRC at approximately 70 to 75 years in the upright position but only 44 in the supine position (Fig. 2.13). This is a major factor in the decrease of arterial Po_2 with age (page 183).

PRINCIPLES OF MEASUREMENT OF COMPLIANCE

Compliance is measured as the change in lung volume divided by the corresponding change in the appropriate pressure gradient, there being no gas flow when the two measurements are made. For lung compliance the appropriate pressure gradient is alveolar/intrapleural (or intrathoracic) and for the total compliance alveolar/ambient. Measurement of compliance of the thoracic cage is seldom undertaken but the appropriate pressure gradient would then be intrapleural/ambient, measured when the respiratory muscles are totally relaxed.

Volume may be measured with a spirometer, a body plethysmograph or by integration of a flow rate obtained from a pneumotachogram. Static pressures can be measured with a simple water manometer but electrical transducers are now more common. Intrathoracic pressure is normally measured as oesophageal pressure which, in the upright subject, is different at different levels. The pressure rises as the balloon descends, and the change is roughly in accord with the specific gravity of the lung (0.3 $g.ml^{-1}$). It is convention to measure the pressure 32 to 35 cm beyond the nares, the highest point at which the measurement is free from artefacts

due to mouth pressure and tracheal and neck movements. Alveolar pressure equals mouth pressure when no gas is flowing: it cannot be measured directly.

Static Compliance

In the conscious subject, a known volume of air is inhaled from FRC and the subject then relaxes against a closed airway. The various pressure gradients are then measured and compared with the resting values at FRC. It is, in fact, very difficult to ensure that the respiratory muscles are relaxed, but the measurement of lung compliance is valid because the static alveolar/intrathoracic pressure difference is unaffected by any muscle activity.

In the paralysed subject there are no difficulties with muscular relaxation and it is very easy to measure static compliance of the whole respiratory system simply using recordings of airway pressure and respiratory volumes. However, due to the uncertainties about interpretation of the oesophageal pressure in the supine position (Fig. 2.5), there is usually some uncertainty about the pulmonary compliance. For static compliance it is therefore easier to measure *lung* compliance in the upright position, and *total* compliance in the anaesthetized paralysed patient who will usually be in the supine position.

Dynamic Compliance

These measurements are made during rhythmic breathing, but compliance is calculated from pressure and volume measurements made when no gas is flowing, usually at end-inspiratory and end-expiratory 'no-flow' points. The usual method involves creation of a pressure–volume loop by displaying simultaneously as *x*- and *y*-coordinates the required pressure gradient and the respired volume. In the resultant loop, as in Figure 2.14, *A*, the no-flow points are where the trace is horizontal and the dynamic compliance is the slope of the line joining these points.

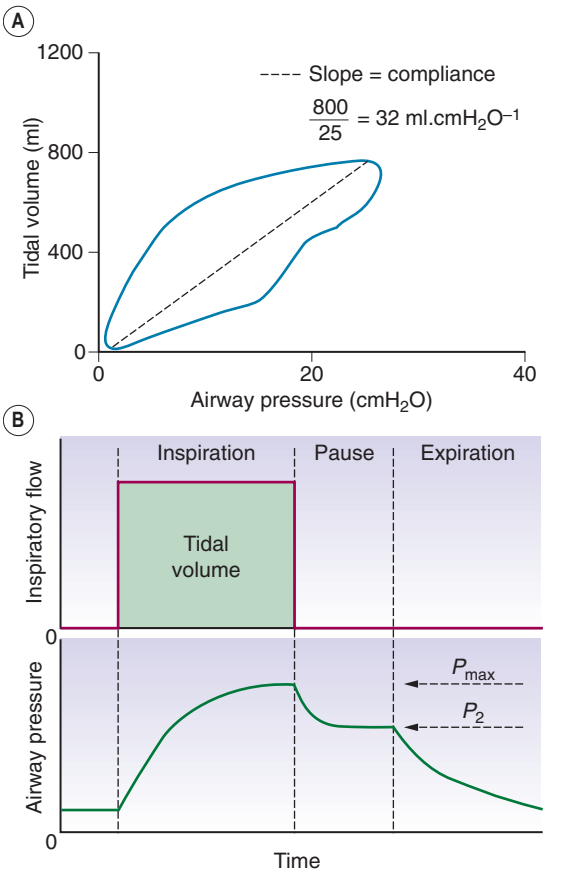

FIG. 2.14 Automated measurement of compliance during intermittent positive pressure ventilation. **(A)** Dynamic compliance. Simultaneous measurement of tidal volume and airway pressure creates a pressure/volume loop. End-expiratory and end-inspiratory no-flow points occur when the trace is horizontal. At this point, airway pressure and alveolar pressure are equal, so the pressure gradient is the difference between alveolar and atmospheric pressure. Total respiratory system compliance is therefore the slope of the line between these points. Note that in this patient compliance is markedly reduced. **(B)** Static compliance. Following an end-inspiratory pause the plateau pressure is recorded (P_2) and along with tidal volume the static compliance easily derived. This manoeuvre also provides an assessment of respiratory system resistance by recording the pressure drop ($P_{max} - P_2$) and the inspiratory flow immediately before the inspiratory pause (see page 47).

Automated Measurement of Compliance

In a spontaneously breathing awake patient lung compliance measurement is difficult because of the requirement to place an oesophageal balloon. However, in anaesthetized patients or those patients receiving intermittent positive pressure ventilation (IPPV) in intensive care the measurement of compliance is considerably easier. Many ventilators and anaesthetic monitoring systems now routinely measure airway pressure and tidal volume. This enables a pressure volume loop to be displayed (Fig. 2.14, *A*), from which the dynamic compliance of the respiratory system may be calculated on a continuous breath-by-breath basis. When no gas is flowing during IPPV (at the end of inspiration and expiration) the airway pressure equals alveolar pressure. At this point, the airway pressure recorded by the ventilator therefore equals the difference