

# 18.1.2 Airways and alveoli

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18.1.2 Airways and alveoli 3937 capacity, thus preventing atelectasis. In adults there is no good evidence that the rate of expiration is underactive laryngeal control, but this mechanism may come into action during respiratory illnesses (such as pneumonia), especially if there is marked hypoxaemia. If the upper airway is bypassed, for instance, by tracheostomy or intubation, then other mechanisms come into play to maintain end-expiratory lung volume, such as post-inspiratory contraction of the diaphragm (thus delaying expiration) and shortening of expiratory time (thus starting inspiration again before lung volume has fallen too far). Fig. 18.1.1.6 is from a tracheotomized dog with areas of atelectasis. This shows how once laryngeal braking is denied to the animal, expiration proceeds faster, lung volume falls, and expiratory time is shortened to produce tachypnoea. This reflex was not present when the areas of atelectasis had resolved. The clinical correlate of this is sometimes seen as an expiratory grunt in babies who have a respiratory illness. Intubation may worsen gas exchange in this situation unless positive end-expiratory pressure is also applied.

Disorders of the larynx

Recurrent laryngeal nerve paralysis

Complete paralysis of the recurrent laryngeal nerve gives permanent hoarseness of the voice, and the affected cord assumes a position midway between full abduction and adduction. The cord is floppy and can be moved passively very easily, being 'sucked' towards the midline during inspiration and blown open during expiration. The unparalysed cord may eventually compensate to some degree and move nearer the paralysed cord, improving the voice. If paralysis of the recurrent laryngeal nerve is incomplete, the affected cord may take up the adducted position, presumably because the fibres running to the abductors are damaged first. When there is bilateral damage to the recurrent laryngeal nerves, loss of adequate abduction causes inspiratory stridor as the cords are passively drawn together.

Laryngospasm and inducible laryngeal obstruction

Laryngospasm should be considered in patients with sudden onset breathlessness and stridor due to rapid and complete laryngeal closure. The most common presentation is with variable exertional breathlessness and

inspiratory stridor that is often mistaken for a wheeze, and often observed on exertion. The condition is often misdiagnosed as asthma, but further complicated as it may coexist in up to 25% of patients with asthma. In severe cases it is associated with hypoxia, and in some instances with loss of consciousness. The condition is often associated with psychological or psychiatric factors, but may also be precipitated by drugs such as baclofen, haloperidol, neuroleptics, and  $\beta$ -agonists. The diagnosis can be made by nasendoscopy, which allows the vocal cords to be visualized during exercise (usually on a static bicycle), or by demonstration of reversible or variable flattening of the inspiratory portion of the flow volume loop during an episode of stridor. Speech therapy, relaxation, and breathing techniques are the mainstay of treatment. There is also a distinct entity of inducible laryngeal obstruction, which is associated with exercise. The symptoms occur rapidly on the onset of exercise and subside on cessation of exertion. In other cases there may be a hypersensitivity of the larynx leading to persistent cough in response to stimuli such as gastro-oesophageal reflux or chronic rhinosinusitis.

**FURTHER READING** Brouillette RT, Thach BT (1979). A neuromuscular mechanism maintaining extrathoracic airway patency. *J Appl Physiol*, 46, 722-9. Gautier H (1973). Control of the duration of expiration. *Resp Physiol*, 18, 205-21. Horner RL (1991). Evidence for reflex upper airway dilator muscle activation by sudden negative airway pressure in man. *J Physiol*, 436, 15-29. Matthew OP, Sant 'Ambrogio GS (1988). Respiratory function of the upper airway. In: *Lung biology in health and disease*, Vol. 35. Marcel Dekker, New York. Remmers JE, Bartlett D (1977). Reflex control of expiratory airflow and duration. *J Appl Physiol*, 42, 80-7.

**18.1.2 Airways and alveoli** Peter D. Wagner and Pallav L. Shah **ESSENTIALS** The lung is the organ of gas exchange, providing the means of transferring oxygen ( $O_2$ ) from the air to the blood by passive diffusion for subsequent distribution to the tissues, and of similarly removing metabolically produced carbon dioxide ( $CO_2$ ) from the blood, which is then exhaled to the atmosphere. A large surface area of contact between alveolar gas and capillary blood is required to ensure sufficient gas flux across the blood-gas barrier to meet metabolic demand: the lungs contain about 300 million very small (radius c.150  $\mu m$ ) alveoli. After the main stem bronchi have arisen from the trachea, the airways continue in a branching pattern with each bronchus dividing into two to five branches. The smaller airways have essentially (a) Inspiration Expiration 5 s (b) Fig. 18.1.1.6 Recorder tracings in a dog with atelectasis showing the effect of switching from upper airway to tracheostomy breathing (arrow at a) and from tracheostomy to upper airway breathing (arrow at b). The signal from an inductive plethysmograph measuring movement of both the ribcage and abdomen which represents lung expansion and contraction.

**Section 18 Respiratory disorders 3938** a dichotomous branching pattern until the alveoli are reached. Successive branching of connected conducting pipes to the sixteenth generation yields in the order of 50 000 to 100 000 airways (called terminal bronchioles), each of which supplies a functional lung unit comprising a further seven generations of divisions (three divisions of respiratory bronchioles, then alveolar ducts, finally alveoli). The lungs are enclosed within the thoracic cavity. Inspiration is driven by contraction of the intercostal muscles and the diaphragm, which expands the ribcage in both anteroposterior and lateral dimensions, such that the pressure inside the thoracic cavity but external to the lungs is reduced to below that of the air, which is thereby drawn in. Expiration to return lung volume to functional residual capacity after inspiration occurs by elastic recoil. Lung diseases of many types commonly affect each of the steps involved in gas exchange, and the clinical consequences can usually be readily understood if the structure-function relationships are known. The organ of gas exchange The lung is the organ of gas exchange, providing the means of transferring oxygen ( $O_2$ ) from the air to the blood for

subsequent distribution to the tissues. At the same time, it enables removal of metabolically produced carbon dioxide (CO<sub>2</sub>) from the blood, which is then exhaled to the atmosphere. Not just in health, but also in lung disease, the volumes of O<sub>2</sub> taken up and CO<sub>2</sub> removed by the lung per minute must equal the rate of O<sub>2</sub> consumption and CO<sub>2</sub> production by the whole body. The lung will also exchange any other gas that is presented to it, but the principles involved—passive diffusion—mirror those for O<sub>2</sub> and CO<sub>2</sub>. Quantitative but not qualitative differences occur in how such gases (e.g. anaesthetic agents, carbon monoxide, toxic gases inhaled by accident) are handled by the lung. These differences stem from the means by which any particular gas is transported in the blood; whether in a simple physical solution alone, or also in some chemical combination with molecules such as haemoglobin. The principles are similar for gas uptake into blood and elimination from the blood. In fact, because gas exchange occurs by passive diffusion, whether a gas is taken up from the air into the blood or eliminated from the blood into the air depends simply on the partial pressures of the gas on each side of the blood-gas barrier, the 0.3 µm thick tissue layer separating alveolar gas from pulmonary capillary blood. For the transfer of a gas from the environment to the blood to occur, the gas in question must first be brought to the alveolar blood-gas barrier by the process of ventilation. Diffusion across this barrier then occurs at a rate proportional to (1) the alveolar surface area available and (2) the partial pressure difference between alveoli and blood, and inversely proportional to the thickness of the barrier, in concordance with the rules of simple passive diffusion. The gas molecules, now present dissolved physically in plasma, also distribute into the red cells. Depending on the gas, chemical associations may occur—with haemoglobin in the case of O<sub>2</sub>, CO<sub>2</sub>, carbon monoxide (CO), and nitric oxide (NO), and through transformation to bicarbonate ion for CO<sub>2</sub>. The last element of the exchange process now occurs—the transport of the gas in blood pumped by the heart through the systemic circulation to the tissues of the body. This chapter focuses on the first two of these three steps in gas exchange—ventilation and diffusion. A separate chapter deals with the third step—the pulmonary circulation (see Chapter 16.15.1). The structural basis of ventilation and diffusion, and the associated functional consequences, will be presented with particular emphasis on implications for disease. Lung diseases of many types commonly affect each of the steps involved in gas exchange, and the clinical consequences can usually be readily understood if the structure-function relationships are known.

**Basic airway and alveolar design** In essence, the lung is a balloon undergoing cyclical inflation and deflation (ventilation, or tidal breathing) around some partially inflated state; the main anatomical elements are shown in Fig. 18.1.2.1. The gas-filled interior of the balloon corresponds to the alveolar gas spaces of the lung. The thin wall of the balloon may be likened to the blood-gas barrier, with the pulmonary capillary network imagined as covering the balloon's surface, separated from the interior (alveolar) gas by the elastic material making up the balloon's wall. The lung is inflated through the trachea with each inspiration, thus bringing fresh air (21% O<sub>2</sub>, no CO<sub>2</sub>) to the alveoli. This fresh gas is rapidly mixed with the resident gas already present. This resident gas is partially depleted of O<sub>2</sub> by ongoing diffusion of O<sub>2</sub> into the capillaries, while at the same time CO<sub>2</sub> is evolved into the gas from the capillary blood. Each inflation, by bringing fresh air into the alveoli, slightly increases alveolar P<sub>O2</sub> and decreases alveolar P<sub>CO2</sub>. Each deflation moves some of this alveolar gas back to the environment. This rids the lung of some CO<sub>2</sub>, but also removes some O<sub>2</sub>, albeit at Trachea Hilum (left) Parietal pleura Intrapleural space R and L of the diaphragm Pulmonary artery Lobar branchi Pulmonary vein Visceral pleura Right lung Left lung Fig. 18.1.2.1 The right and left lungs are separately encased within the thorax, and each is covered by a visceral pleural membrane. This is continuous with the parietal pleural membrane which lines the interior thoracic cavity, and the thin fluid-filled space between the

visceral and parietal pleurae constitutes the intrapleural space. The hila of the two lungs contain the mainstem bronchi, and accompanying pulmonary arteries and veins. The mainstem bronchi join at the carina to form the trachea. The pulmonary arteries emanate from the right ventricle; the pulmonary veins empty into the left atrium. Within the lungs, the airways and blood vessels continue branching for approximately 20 generations. The major muscle of inspiration, the diaphragm, consists of two domes upon which the right and left lungs sit, and which separate the thoracic and abdominal contents.

18.1.2 Airways and alveoli 3939 lower concentrations than in room air. In normal quiet breathing, alveolar O<sub>2</sub> concentration averages about 16% over a respiratory cycle, whereas that of CO<sub>2</sub> is about 5%, and a long-term steady state of gas exchange is achieved. Because the process of gas exchange depends on simple, passive diffusion, a large area of contact between alveolar gas and capillary blood is required to ensure sufficient gas flux across the blood-gas barrier to meet metabolic demand. The balloon analogy, while useful as an initial concept, thus exhibits a major difference from how the real lung is configured. The real lung has its total gas volume constituted not as a single balloon-like gas chamber, but as a very large number (about 300 million) of very small, almost spherical, balloons or alveoli (radius,  $r$ , c.150  $\mu\text{m}$ ). Since the volume ( $V$ ) of a sphere is  $V = (4/3) \times \pi \times r^3$ , while its surface area ( $A$ ) is  $A = 4 \times \pi \times r^2$ , dividing a lung of a given volume (given because the lung must fit within the thoracic cage) into many small alveoli allows a much larger total surface area than if the lung were indeed a single large chamber. Given that a typical value for  $V$  is 4000 ml, a single sphere of this volume would have a radius of about 10 cm and a surface area of about 1200 cm<sup>2</sup>, whereas 300 million alveoli, each with a radius of 150  $\mu\text{m}$  have the same total volume but have a total surface area of about 800 000 cm<sup>2</sup>, which approximates the area of a tennis court. Given the laws of diffusion, maximal pulmonary O<sub>2</sub> exchange would be insufficient for life were the lung a single chamber. The lungs inside the thoracic cavity As with a balloon, the lung cannot inflate itself (although, as an elastic structure, once inflated it is capable of unassisted deflation just like a balloon). Inflation requires creation of a pressure difference between the outside and inside of the lung, pressure being higher inside. This may be accomplished in one of only two ways. One is by positive pressure inflation, typical of most clinical ventilators that are connected to the trachea and produce inflation by mechanically increasing intratracheal airway pressure. Spontaneous breathing throughout normal life does not happen in this way, and so the only possibility of normally achieving lung inflation is by the second option—that of decreasing the pressure around the lungs below that of the surrounding air. This is accomplished by encasing the lungs within the closed thoracic cavity, and having the muscles in the wall of this cavity (the intercostal muscles and the diaphragm) contract when inflation is desired. Contraction of these muscles moves the diaphragm caudally and expands the ribcage in both anteroposterior and lateral dimensions. As a result, the pressure inside the thoracic cavity but external to the lungs (i.e. within the intrapleural space) is reduced to below that of the air. Since the alveolar tissue is extremely thin and easily deformable, the pressure within the alveolar gas spaces is also reduced to below that of the air, and thus inflation occurs as a result of a hydrostatic pressure gradient from the mouth to the alveoli. Inflation in the course of normal tidal breathing usually commences from a state of partial lung inflation that reflects that particular volume of the lung at which its own elastic recoil tendency to collapse is exactly balanced by the opposite, natural tendency of the ribcage to expand outwards. This volume is known as the functional residual capacity (FRC) and because it reflects recoil balance between lung and chest wall, it is the only volume which can be maintained without muscular effort. Thus, to either inhale

above FRC or to exhale below FRC requires respiratory muscle contraction, but the return to FRC from either higher or lower volumes can be passive, stored elastic energy provided by respiratory muscle contraction from the preceding active volume change being used to reverse the transpulmonary pressure difference and enable gas flow from the alveoli to the mouth. Clinical significance Elastic properties and lung volume If the elastic properties of either the lungs or the chest wall are altered by disease, FRC will change. Should the lungs become less elastic, typically seen in emphysema due to disorganization of the elastin and collagen fibres making up much of the alveolar wall structure, the tendency for the lung to collapse is less, and the lung/chest wall recoil balance shifts to a higher lung volume, thus increasing FRC. By contrast, diseases characterized by proliferation of alveolar wall elements—collagen in particular—renders the lung more elastic and thus collapsible, shifting FRC to lower values. These changes in FRC may be used to aid in diagnosis and in following the natural history and response to treatment of such diseases, since FRC is readily measured in the pulmonary function laboratory by either plethysmography or helium dilution methods. Changes in FRC also have important implications for lung function, discussed later in this chapter. While FRC is a key volume upon which to focus, the lung can normally be inflated to well above FRC, and also deflated to considerably below FRC. At maximal inflation, lung volume is referred to as the total lung capacity (TLC), while at maximal deflation, lung volume is called the residual volume (RV). Of major significance, RV is well above zero volume. As will be apparent, if all alveoli could be fully emptied of gas, they would be very difficult to reinflate to allow resumption of gas exchange, due to surface tension. The difference between TLC and RV is called the vital capacity (VC). As with FRC, each of these volumes is readily measured during routine pulmonary function testing, and together they provide a simple yet informative profile useful in characterizing many lung diseases and their progress. Unlike some physiological variables, such as arterial pH or haemoglobin concentration, all of the above volumes depend to a major extent on body size. They also depend to a lesser degree on gender (smaller in females), age (deterioration with ageing), bodily habitus (often smaller in the obese), and ethnicity. Many tables of normal values have been published, and interpretation must allow for all of the determinants mentioned already here. Trachea, main bronchi, and pleura For all 300 million alveoli to participate in the gas exchange process, each must be connected to the environment by an air pathway. The analogy now changes from a balloon to a tree. Imagining an upside-down tree, the main trunk represents the trachea, the single common airway segment through which inhaled and exhaled gas from all alveoli must pass. The upper end of the trachea begins at the lower margin of the larynx. The trachea lies anteriorly in the neck and chest, passing caudally in the midline retrosternally to the level of about the sternal attachment of the second rib. There it divides into left and right mainstem bronchi, each smaller and shorter than the trachea. These two airways angle caudally and laterally within the upper mediastinum to enter the left and right lungs at the left

Section 18 Respiratory disorders 3940 and right hilar regions, respectively, and they divide into the lobar bronchi, three on the right to feed the right upper, middle, and lower lobes, and two on the left to feed the two left lobes, upper and lower. Note that the two hilar regions are the only normal points of actual connection of the left and right lungs to any thoracic structures, and also contain the large pulmonary arteries and veins, lymphatics, and nerves. The entire remaining lungs, while opposed against the chest wall, are not connected to it and are able to slide easily over the inner chest wall surface. This inner surface is covered by the parietal pleural membrane, and the outer surface of the lungs is similarly covered by the visceral pleural membrane. These two pleural mem-

branes are joined at the hilar regions to form a fully enclosed sac that separates the lung and chest wall. The left and right pleural sacs do not communicate with each other, and normally contain only a very thin layer of plasma-like fluid and no gas at all. This arrangement may be pictured by imagining a sealed, but empty, plastic sandwich bag from which all air has been expelled and which contains a very small volume of water. If one's right hand is balled into a fist and invaginates this bilayered bag against the cupped left hand, we have the analogy to the right (or left) lung and chest wall. The balled right fist is the lung; the right wrist and forearm represent the hilar structures. The cupped left hand is the chest wall, and the two layers of the closed sandwich bag form the pleural membranes.

**Clinical significance Mainstem bronchial branching angles** The mainstem bronchial branching from the trachea is not quite symmetrical. The right mainstem bronchus continues caudally a little more directly in line with the trachea above it than does the left, which angles laterally more sharply. As a result, accidentally inhaled foreign bodies more frequently lodge in the right than left lungs. For similar reasons, advancing an endotracheal tube too deeply may cause it to lodge in the right mainstem bronchus rather than where intended—the trachea. This will result in lack of ventilation of the left lung, and if not recognized, hypoxaemia from continued perfusion of this unventilated lung with venous blood, and ultimately left lung collapse (over minutes to hours).

**The intrapleural space and pneumothorax** The pressure within the pleural space (i.e. between visceral and parietal pleural surfaces) is normally subatmospheric because of the above-mentioned counterbalancing inward lung and outward chest wall recoil forces. This prevents lung collapse. Disruption of either the visceral or parietal pleura (i.e. pneumothorax) allows air to enter the pleural space, increasing the intrapleural pressure back to atmospheric. This results in collapse of the lung, with abolition of ventilation even if chest wall muscle contraction continues. Gas exchange therefore ceases, threatening life. In humans, since the right and left lungs are encased in separate pleural sacs, if one side suffers pneumothorax, gas exchange can usually be maintained by the other. Pneumothorax can occur from rupture of lung surface alveoli in predisposed individuals, or from chest wall trauma in anyone. Whether the source of the intrapleural air is alveolar gas as in the former case or room air in the latter makes no difference. However, depending on conditions, intrapleural air pressure may actually rise above that of room air. This situation, the tension pneumothorax, can arise whenever air enters the pleural space via a valve-like mechanism, when the patient's respiratory effort or that of a mechanical ventilator can lead to intrapleural pressure rising well above atmospheric. The lung collapses, but the (increasingly desperate) respiratory effort or mechanical ventilator keeps pumping air into the pleural space via the torn lung surface. This is a true emergency requiring immediate needle puncture of the chest wall of the affected side to relieve the built-up pressure. If this is not done, the high intrathoracic pressure compresses and distorts the mediastinum and vena cavae, impeding venous return. Both pulmonary gas exchange and the circulation fail, and death follows rapidly.

**Mediastinal shifts** The separation of the right from left pleural spaces provides for lateral movement of the mediastinum should there be a difference in mechanical properties of the right and left lungs or their associated pleural spaces or chest wall structures. For example, fibrosis of the right lung, or alternatively its collapse from complete airway obstruction, will reduce the volume of intrathoracic contents and therefore pressure on that side, and mediastinal contents will shift towards the right, visible on chest radiography. In fact, the trachea may also be shifted from its normal midline location in this direction, evident on clinical examination of tracheal position just above the suprasternal notch. Conversely, a pleural effusion on the right or a right pneumothorax (see next section) may raise intrathoracic pressure above that on the left, and have the opposite effects on mediastinal and tracheal position. The bronchi and bronchioles After the

mainstem bronchi have arisen from the trachea, the airways continue an essentially dichotomous branching pattern until the alveoli are reached. Thus, successive branching yields in the order of 50 000 to 100 000 airways (called terminal bronchioles) that constitute the sixteenth generation ( $2^{16} = 65\,536$ ). The entire collection of airways from the trachea to these last bronchioles before alveoli begin forms a system of connected conducting pipes needed to deliver gas between the alveoli and the environment during ventilation (Fig. 18.1.2.2). As with the branching of a tree, both the diameter and the length of each successive branch fall. The trachea typically is 12 cm long and 2 cm in diameter. By contrast, the typical terminal bronchiole is just 1–2 mm long and 0.6 mm in diameter. Airflow is normally mostly laminar (except for that in the upper airways) and therefore is governed by Poiseuille's law of fluid dynamics. The essence of this law is that resistance to airflow depends inversely on the fourth power of the airway radius, but varies only in direct proportion to airway length. As airways become both narrower and shorter with increasing branching, it is evident that resistance of a single airway increases dramatically because of the dominating effect of the fourth power of the radius. However, if one asks how the entire system behaves by plotting how airway pressure must fall from trachea to generation 16 (e.g. during steady inspiratory flow), one must allow for the fact that all airways of any single generation are arranged in parallel with one another. Because branching is essentially dichotomous, there are twice as many airways in any given generation as in the one before. Thus, total airway resistance of any one generation is diminished in proportion to the exponentially increasing number of airways as branching continues. This actually overcomes the fourth

18.1.2 Airways and alveoli 3941 power disadvantage of Poiseuille's law, such that most of the pressure drops, or put another way, most of the system airway resistance is associated with the first few generations despite their large individual airway size. Another way to understand this somewhat counterintuitive result is to consider the sum total of the cross-sectional areas of all airways in a single generation. This is of course the area of a typical airway multiplied by the number of airways in that generation. That number is low for the first few generations, but then rises dramatically because of the exponentially increasing number of airways in each generation. Airway resistance of a generation therefore falls from the first few generations to the terminal bronchioles. The summed total volume of gas contained within all 16 generations of these conducting airways is only about 150 ml, despite their prodigious number. Clinical significance Dead space The interposition of airways between the mouth and the alveoli creates a volume of gas (c.150 ml as mentioned) called the anatomical dead space. The gas in this dead space simply passes back and forth during inspiration and expiration without contributing to gas exchange since the conducting airways contain no alveoli in their walls. It constitutes a penalty since it adds an obligatory 150 ml volume requirement to every breath taken. This is of no importance in health, but in patients with severe lung disease such as chronic obstructive lung disease or fibrosis, the energy cost of overcoming either high resistance in obstructed airways or low compliance of fibrotic lung tissue, and of thus mounting adequate ventilation, may be greatly increased. Then, the need to breathe some 150 ml more per breath than actually required for alveolar gas exchange can be clinically important as a factor contributing to respiratory failure. Recognition of this has led to the use of transtracheal insufflation of air, which permits the anatomical dead space of at least the upper airways to be circumvented and reduces the ventilation necessary for any given activity. Particle deposition Ventilation involves breathing some 6–10 litres of air every minute of our lives. Air contains much particulate matter of very small size. Depending on particle size, rate of gas flow in the airways, and airway geometry, such particles may move harmlessly in and out with the next

breath or they may be deposited somewhere on the epithelial surface in the bronchial tree. To the extent that they do deposit and are chemically or physically harmful to tissue, they can be responsible for disease. Pneumoconioses, chronic obstructive pulmonary disease, bacterial and viral infections, asthma, and other diseases may all be initiated and/or affected by such mechanisms. The dividing airway structure described here already combines ever-diminishing individual airway diameter with ever-diminishing gas velocity (due to increasing summed cross-sectional airway area of all airways in a generation) as branching continues. As airways narrow and flow velocity falls, the chance of airborne particles being deposited on airway walls increases. It is for this reason that coal dust, for example, settles mostly in the terminal bronchiolar region deep within the branching system. Thus, the basic nature of gas exchange, demanding the branching network of airways described, leads to intrinsic vulnerability to disease from airborne particulate matter.

10000 Trachea  
Bronchi  
Bronchioles  
Terminal bronchioles  
Respiratory bronchioles  
Alveolar ducts  
Alveolar sacs

Transitional and respiratory zones  
Conducting zone

Z	0	1	2	3	4	5	16	17	18	19	20	21	22	23
(a)	8000	6000	4000	2000	0	0	5	10	20	15	25	Total airway cross-sectional area (cm <sup>2</sup> )		
(b)	Alveoli													

Trachea  
Fig. 18.1.2.2 (a) This shows a stylized model of the branching of the airways from trachea to alveoli, encompassing some 23 generations of branching. The first 16 generations contain no alveoli and are purely conducting airways, but the next seven generations contain progressively more alveoli in the airway walls and serve the dual purpose of conducting air to the alveolar sacs and also providing gas exchange. (b) Total cross-sectional area of each generation shown in (a). This is obtained by multiplying the average cross-sectional area of a single airway by the number of airways in the particular generation. The cross-sectional area is small throughout the conducting zone (first 16 generations), but then increases exponentially in the respiratory zone. The implications are that the forward velocity of inspired gas falls dramatically in the respiratory zone such that diffusion becomes the faster mode of molecular movement. In addition, this diagram implies that during flow between the mouth and alveoli, most of the airway resistance resides in the first 15 generations. Adapted from Weibel ER (1984). Pathway for oxygen: structure and function in the mammalian respiratory system. Harvard University Press, Cambridge, MA, with permission.

Section 18 Respiratory disorders 3942 Mucociliary function As seen commonly in evolutionary responses to deleterious phenomena, a protective system has been developed to mitigate the consequences of particle deposition in the airways. This is the mucociliary apparatus. It has several components. There are sub-mucosal glands in the walls of the conducting airways that secrete mucus into the airway lumen when stimulated by irritant signals. These glands are supported by other secretory cells in the epithelium of the airways such as goblet cells. The epithelial cells that line the entire conducting airway system are ciliated, and they function in a coordinated manner, beating rhythmically to move the secreted mucus upward from smaller to larger airways. The primary purpose of the mucus is to trap inhaled particulates before they can reach and damage the airway and lung tissues themselves. This upwardly transported mucus is clinically evident as sputum. The volumes of sputum produced normally are so small as to be unnoticeable, and are usually swallowed. However, inhalation of toxic irritants, infectious agents, and other particles will rapidly increase the volume of sputum to noticeable levels, and chronic airway inflammation from, for example, cigarette smoking will produce chronically increased amounts of mucus that give rise to the syndrome of chronic bronchitis. It is especially noteworthy that in asthma, not only is the volume of mucus increased, probably from airway inflammation, but its composition is altered, rendering it much more tenacious and difficult to eliminate by the ciliary system. Mucus thus

accumulates in the airway lumina, particularly those of the smaller conducting bronchioles, creating mucus plugs that cause obstruction to airflow and marked reduction in ventilation of alveoli lying distal to them. When this occurs, asthma is often refractory to usual pharmacological therapy, and patients dying from asthma universally exhibit widespread airway mucus plugging.

**Dynamic airway compression** Another intrinsic physiological problem of the branching airway system within the chest is related to the mechanical nature of respiration—the need for inflating and deflating the lung by altering the pressure around it—combined with the fact that the airways are not rigid tubes. The airways are thus susceptible to expansion and compression (and therefore to collapse) on inspiration and expiration, respectively. The intrapleural pressure may be transmitted to the conducting airways, and while reduction in this pressure on inspiration will only distend the airways, allowing air to flow more freely, opposite effects during expiration may not be innocuous. Passive expiration—that is, expiration fuelled only by the elastic energy stored in the lung tissue from the previous inspiration, without active expiratory muscle effort—does not compress the airways because the intrapleural pressure remains subatmospheric. However, active expiratory muscle contraction, as occurs during a forced expiratory manoeuvre and during heavy exercise, leads to compression of the airways because intrapleural pressure is raised to above atmospheric. In fact, the greater the expiratory effort made, the greater the increase in intrapleural pressure and the degree of airway compression. Because of this, flow rates during forced expiration cannot be increased by making a greater muscular effort: any greater driving pressure for expiratory flow is balanced by the increased resistance resulting from more compression. As a result, even in normal subjects, expiratory flow of air under these conditions is limited by this phenomenon, known as dynamic compression, which is illustrated in Fig. 18.1.2.3. The loss of elastic recoil in emphysema, mentioned here earlier in the context of its effects on FRC, also has a major influence on dynamic compression. The airways are much more susceptible to dynamic compression (discussed next), such that even breathing at rest with just small increases in intrapleural pressure from active expiratory muscle contraction may be subject to flow limitation by this mechanism. When this problem is compounded by the separate phenomenon of increased airway luminal mucus from chronic inflammation induced by cigarette smoking, it is easy to understand how chronic obstructive lung disease (emphysema and chronic bronchitis) has airway obstruction as its major disturbance. In the consideration of dynamic compression it is important to note that the alveoli are not physically independent of one another or of the conducting airways, which run within the lung parenchyma from the lobar bronchi all the way out to the terminal bronchioles. The alveoli share walls in their mutual attachments, and the alveoli beside any intrapulmonary conducting airway are physically connected to the outside of that airway wall. A good analogy for how the alveolar parenchyma is configured comes from (a) Bronchiole Mouth

–10 –10 –10 –10 –10 –10 0 0 0 0 (b) Airflow

- 30
- 30
- 30
- 40
- 30
- 30
- 30
- 35

- 30 Bronchiole Dynamic compression Intrapleural space Mouth Intrapleural space

Fig. 18.1.2.3 Diagram to explain dynamic compression during expiration. (a) This depicts intrapleural, alveolar, and airway pressures while breath holding with an open glottis at total lung capacity. Due to lung elasticity, intrapleural pressure is negative ( $-10$  cmH<sub>2</sub>O), but because of breath-holding there is no flow, and pressure in the airways and alveoli equals that at the mouth,  $0$  cmH<sub>2</sub>O. Immediately after commencing a forced expiration from total lung capacity (b), intrapleural pressure is high due to expiratory muscle contraction ( $+30$  cmH<sub>2</sub>O). Alveolar pressure is even higher due to  $10$  cmH<sub>2</sub>O of lung elastic recoil pressure. However, due to flow resistance, pressure falls from  $+40$  gradually to  $+30$  as shown. At this point, intrapleural pressure equals intraluminal pressure and immediately downstream dynamic compression occurs as airway pressure falls even further and is now less than intrapleural pressure.

18.1.2 Airways and alveoli 3943 examining the cut surface of a sponge, where the myriad air cells are surrounded by thin tissue walls. Every wall serves two adjacent air cells, and the overall structure is solid (rather than like the leaves of the tree which are physically independent of each other even while being connected to the same dividing network of branches). The net result of this matrix of alveolar and airway connections is that when the lung is inflated, the elastic tension in the parenchyma exerts radial traction on the conducting airways, increasingly so as the lung is further inflated. This stiffens the airway walls and acts to oppose dynamic compression during active expiration. That maximal expiratory flows are greater at high than low lung volumes is explained by the greater radial traction at high volumes as the alveoli are stretched more. The walls of the larger conducting airways (the trachea and first few generations of bronchi) are reinforced with cartilage rings that further help to counter the forces favouring dynamic compression. However, the smaller conducting airways do not enjoy this protection, and it is in the smaller airways that dynamic compression usually has its major effects. Airway smooth muscle All generations of conducting airways contain smooth muscle cells. When stimulated to contract, their concentric arrangement leads to reduction in airway lumen size, and airway obstruction results. While not a significant effect in normal individuals, patients with asthma have hyperresponsive airway smooth muscle that contracts in response to the inflammatory reaction usually present in the asthmatic airway walls. This is a major mechanism of airway obstruction in asthma, and is the basis of the mainstay therapy in this disease—bronchodilators. For reasons that remain unclear, smooth muscle contraction does not occur to the same degree in all airways of the asthmatic lung: there are different degrees of obstruction both with respect to airway generation number and among airways of a given generation. Ventilation of alveoli is thus very uneven, with many alveoli being very poorly supplied with air, yet others are well-supplied. Gas exchange becomes inefficient as a result, and arterial hypoxaemia is seen. Airway smooth muscle also contracts when local CO<sub>2</sub> concentrations fall. This happens commonly in pulmonary thromboembolism, when vascular obstruction results in focal areas of hypoperfusion that remain relatively overventilated, such that their local alveolar CO<sub>2</sub> tension falls. This, possibly in concert with bronchoactive inflammatory mediators released in association with the embolic event, can produce local airway smooth muscle contraction and airway obstruction. This might tend to better matching of local ventilation with blood flow, but the benefit is generally small, and local bronchoconstriction can manifest as wheezing, which should not be mistaken for asthma. Dynamic tests of airflow All of the traits of the branched structure of the airways and their interconnectedness need to be considered if one is to understand common pulmonary function tests. How the 'static' lung volumes (FRC, TLC, VC, and

RV) are affected by changes in elastic recoil are discussed earlier, but such measures form only a part of standard pulmonary function testing. Usually included are 'dynamic' tests that measure expiratory and inspiratory gas flow rates, conventionally during manoeuvres wherein the patient is asked to make a maximal inspiratory or expiratory muscle effort. These are discussed in Chapter 18.3.1.

**Distribution of ventilation** The extremely large number of very small respiratory bronchioles creates an environment in which alveoli distal to each bronchiole become susceptible to impaired ventilation. Small intrinsic or pathological reductions in airway diameter of such bronchioles can impair distal ventilation substantially. When the effects of variation in mucus secretion, bronchial smooth muscle tone, and radial traction are added to this inherently vulnerable system, it is surprising that the distribution of ventilation to the 300 million alveoli is as uniform as it is. Were it not, there would probably be considerable hypoxaemia, even in health. This topic is discussed further next.

**The parenchyma distal to the terminal bronchioles** The terminal bronchioles (sixteenth generation airways) are the final divisions of the wholly conducting airways. They are completely lined with ciliated epithelium, and function primarily as simple conduits for gas, linking the air around us to the alveoli where gas exchange occurs. The next few divisions of the airways result in transitional airways called respiratory bronchioles, so named because they serve a dual role—as continued gas conduits and as the first locations for gas exchange. Respiratory bronchioles are partly lined with ciliated epithelium, but also have small alveolar outpouchings opening directly into the airway lumen. With continued branching of these bronchioles, more and more of the luminal surface is given to the alveolar outpouchings, and less and less to ciliated epithelium. After about three generations of respiratory bronchioles, the airways, while still essentially tubular in shape are made up entirely of alveolar tissue capable of gas exchange, and are called alveolar ducts. These alveolar ducts branch even further into collections of alveoli whose distal end is blind, known as alveolar sacs, at the end of the line of the airway branching system. A diagram of the functional lung unit is shown in Fig. 18.1.2.4.

**Pulmonary artery Terminal bronchiole Pulmonary vein Capillary network Alveoli**

Fig. 18.1.2.4 Diagram of the functional lung unit. The collection of alveoli and associated pulmonary arteries and veins distal to the terminal bronchiole constitutes a functionally homogeneous unit of gas exchange. The mixing of gas among alveoli and of blood in the capillary networks of the alveoli in the unit is sufficiently rapid that gas concentrations are in effect uniform throughout. This unit, also called the acinus, corresponds approximately to generations 17–23 of Fig. 18.1.2.2.

**Section 18 Respiratory disorders 3944** With some seven orders (or division points) of branching between the terminal bronchioles and the final alveoli, together with 16 orders of branching in the conducting airway segment, the whole airway tree consists of about 23 orders or branch points. Due to the alveolar sacs being blind after the final branch point, the process of ventilation must occur as a tidal (back and forth) event, alternately adding air to, and removing alveolar gas from, each alveolus with each breath. **Gas transport** The transport of gas in either direction between the trachea and the last conducting airway takes place principally by convective flow, much as water flowing in a pipe depends on the pressure difference between the two ends of the pipe and the flow resistance of the pipe. Since flow is mostly laminar, velocity profiles are largely parabolic, the flow being highest in the centre of the lumen and lowest at the airway wall, just as is the velocity profile across a quietly flowing river. There are, however, minor additional influences of diffusive movement at the interface between the convective front of each inspiration and residual gas from the previous breath. These interactions, and eddies that develop at each branch point, may assist gas mixing but their effects are physiologically small. Of much more significance is the fact that

the total luminal cross-sectional area of each generation increases exponentially as the airways divide. Since total volumetric flow of gas is the same in each generation, average gas velocity falls reciprocally with the increase in area. By the time inspired gas reaches the first alveoli, forward velocity has dropped to such a low level that random, thermally fuelled molecular motion (i.e. diffusion) becomes a more important mechanism of gas transport than convection. The small size of the alveoli, about 150  $\mu\text{m}$  in radius, means that diffusive mixing of each new breath with gas resident in the alveoli from prior breaths is nearly instantaneous. Although careful physiological studies can show that low-molecular-weight gases mix slightly faster than those of high molecular weight, this turns out to be of essentially no quantitative significance to gas exchange. Even in emphysema, where many alveolar spaces are enlarged, there is evidence that diffusive mixing in alveolar gas is functionally complete and does not pose a gas exchange threat. Gas exchange of more concern for gas exchange is whether all alveoli receive a similar share of each breath. It was pointed out earlier that the intrinsic structure of the lungs makes it vulnerable to ventilatory inequality, and that this has the potential to disrupt gas exchange. Indeed, recent studies of the structural influence on gas distribution reveal that there are sometimes substantial differences in the ventilation of different alveoli. One property of the system that lessens the negative effects of such inhomogeneity on gas exchange is the finding that individual alveoli do not maintain gas exchange differences from closely adjacent alveoli. In fact, a fairly large number of connected alveoli are normally able to function as a single homogeneous unit of gas exchange. This is no doubt due partly to the rapid diffusive movement of molecules throughout the aforementioned alveolar gas, but it is also facilitated by the rich capillary network lying in the wall of each alveolus. The density of capillaries is so great that should flow fall in one, its neighbour can seamlessly take over its gas exchange role without any resultant inefficiency. It turns out that the functional unit of gas exchange, known as the acinus, corresponds approximately to all the alveoli distal to the last terminal bronchiole. Clinical significance The functional lung unit Pathological events, in either the alveoli or the capillaries, occurring at a scale smaller than that of the functional lung unit will not per se have much impact on gas exchange. Thus, a large number of tiny pulmonary emboli each lodging in one capillary of different functional lung units will not impair gas exchange function, while a single large embolus of the same total mass obstructing one much larger vessel might. However, if enough microvessels within functional units become obstructed, their summed effects may become considerable. Surface tension and mechanical instability of the lung Another consequence of the branched nature of the lungs resulting in so many very small alveoli is inherent mechanical instability. The alveolar wall, where it interfaces with alveolar gas, forms a roughly spherical air-liquid interface. In this context, the alveoli may be likened to a mass of soap bubbles lying together. All air-liquid interfaces are subject to surface tension, which in this case will act to minimize the surface area of each bubble. For an enclosed bubble, this tension increases the pressure inside the bubble, with the relationship between the tension and the interior pressure given by the law of Laplace:  $\text{pressure} = 2 \times \text{surface tension}/\text{radius}$ . Thus, pressure inside a small bubble exceeds that inside a larger bubble, and if two such unequal bubbles are in contact and their interiors become connected, the small bubble will collapse into the larger. This process of bubble accretion may continue until the many small soap bubbles have collapsed into a single large one. Small alveoli Based on the opening premise of this chapter, if small alveoli had this tendency to collapse into larger neighbours due to surface tension effects, the end result would be disaster for gas exchange. There would be massive alveolar collapse, and with loss of surface area, sufficient  $\text{O}_2$  exchange to support metabolic needs would not be possible. Only if all alveoli were identical in both size and surface tension would this problem be avoided, but when

300 million alveoli exist, it is impossible to imagine them all being identical, and indeed they are not. The lung avoids this dilemma through two quite separate but complementary mechanisms of stabilization. The first, already mentioned earlier in a different context, is the interconnected nature of the whole alveolar structure. Any tendency for one alveolus to collapse would have to increase the tension on all its immediately connected neighbours. This tension from surrounding alveoli will automatically serve to splint open the alveolus in question, thus opposing its tendency to collapse. This concept, termed alveolar interdependence, is felt to be of considerable importance in maintaining alveolar stability. The second mechanism is the presence of phospholipid molecules that reduce surface tension in the alveolar air-liquid interface. Termed surfactant, and produced in conjunction with proteins from alveolar type II epithelial cells lying free in the

18.1.2 Airways and alveoli 3945 alveolar spaces against alveolar walls, this material reduces surface tension severalfold (Fig. 18.1.2.5). Thus, the surface tension of the alveolar lining fluid is only about 10 mN/m, whereas that of water is some 75 mN/m. Moreover, probably due to molecular realignment of surfactant molecules, surface tension is even lower when lung volume is reduced. Based on the law of Laplace given earlier, this can be seen to be even more advantageous for evening out surface tension differences among alveoli of different size.

**Surfactant** Surfactant is thought to have another crucial role that promotes efficient gas exchange between alveolar gas and capillary blood. Given that adjacent alveoli share a common wall, the tendency for surface reduction in each alveolus will create a force that tends to reduce the interstitial tissue pressure around capillaries in the alveolar wall between the adjacent alveoli. From the Starling relationship that governs water escape out of capillaries in any tissue (based on the transcapillary differences in both hydrostatic and oncotic pressures), reducing pressure around the capillary will lead to increased water escape into the alveolar wall. This could have several deleterious consequences. First, the affected alveolar walls would become stiffer and harder to inflate, tending to reduce lung volume. Second, the tissue separating gas from capillary blood would become thicker, directly impairing diffusive transport between gas and blood. Third, this water would find its way into the pulmonary lymphatics, which begin in the alveolar interstitium and run along the large airways and vessels to the hilar regions, before exiting the lungs and emptying into the superior vena cava. Extra water frequently accumulates in the peribronchial and perivascular spaces and results in their partial compression, reducing distal ventilation, and/or blood flow of subtended alveoli, causing maldistribution of either or both, and rendering gas exchange inefficient. The presence of surfactant is thought to reduce the rate of transcapillary water exchange, and therefore to contribute to efficient gas exchange.

**Clinical significance**

**Impaired surfactant activity** When surfactant is not present, when its rate of renewal is insufficient, or when it is inactivated rapidly, pathological changes can be severe. Best known is the infant respiratory distress syndrome, occurring in otherwise normal premature infants born before the late-maturing surfactant system is functional. Without exogenous surfactant replacement therapy, the condition may be fatal due to alveolar collapse and pulmonary oedema. Surfactant activity is also compromised in the adult respiratory distress syndrome and may compound the disturbances of pulmonary function arising from the primary cause of the pulmonary disease.

**Gravity and lung function** Causes of potential unequal distribution of ventilation or blood flow to the alveoli extend beyond those associated with the intrinsic branching structure of the lungs discussed earlier. In particular, the presence of gravity influences lung function because key components of the lungs have significant weight. The weight of the parenchyma itself, plus the

blood within the alveolar capillaries, feeding arteries and draining veins, together cause the lungs to sag towards the diaphragm in the upright lung sitting at FRC. The upper pole of the lungs is still applied to the parietal pleural surface of the chest wall—there is no pleural airspace created by this gravitational stress. Rather, the rest of the lung is displaced caudally, sagging much like a heavy sweater pegged to a clothes line. As expected, this creates stress in the alveolar walls, more in the uppermost than lowermost alveoli. A good analogy is the toy Slinky—a coiled spring that when hanging vertically under its own weight shows wider separation between adjacent coils at its top than at its bottom. Correspondingly, the uppermost alveoli in the upright lung are larger than the lowermost alveoli. The lowermost alveoli are thus more compliant—that is, able to be further inflated more per unit transpulmonary pressure—than the uppermost alveoli, because the latter are stretched almost to their limit. Accordingly, normal ventilation from FRC results in greater ventilation of the lung bases than of the lung apices. Much the same effect is seen for blood flow: apical blood flow is less than that at the base of the upright lung. In this case it is the weight of the blood itself that is responsible: perfusion depends on pulmonary arterial pressure, which falls linearly with height up the lung. The apex to base differences in perfusion exceed those of ventilation, such that the ratio of ventilation to blood flow is higher at the base than at the apex. Surfactant film Arrows depict net force inward from surface tension in the surfactant film Gas Pulmonary artery or vein Gas Gas Fig. 18.1.2.5 Diagram to indicate potential effects of surface tension on lung structure and function. Three gas-filled alveoli are shown, each lined by a thin film of surfactant. A pulmonary artery or vein is shown in the corner formed where the three alveoli come together. Arrows show the net inward force produced by surface tension, tending to reduce alveolar gas volume and promote atelectasis. In addition, the pressure in the perivascular space around the corner vessel shown will be reduced by these inward surface forces, increasing the pressure difference from inside to outside the vessel lumen and thereby promoting fluid movement from plasma to interstitial space. The presence of surfactant reduces the magnitude of surface tension forces and therefore stabilizes the alveoli against atelectasis and reduces the transmural pressure difference, attenuating transvascular fluid movement.

Section 18 Respiratory disorders 3946 apex than at the base. The local ventilation/perfusion ( $V'A/Q'$ ) ratio determines local alveolar  $P_{O_2}$  and  $P_{CO_2}$ ,  $P_{O_2}$  increasing and  $P_{CO_2}$  falling as the  $V'A/Q'$  ratio increases. Thus,  $P_{O_2}$  at the apex is higher, and  $P_{CO_2}$  lower than at the base. If the  $V'A/Q'$  ratio everywhere was the same, so too would be  $P_{O_2}$  and  $P_{CO_2}$ , and the exchange of  $O_2$  and  $CO_2$  would be maximally efficient. However, the presence of a range of  $V'A/Q'$  ratios (no matter what its cause) results in gas exchange inefficiency and arterial hypoxaemia. Clinical significance Effects of gravity on lung function in disease Although gravity creates  $V'A/Q'$  maldistribution, common disease processes are in large part randomly distributed in the lungs, and their effects on  $V'A/Q'$  matching are generally much greater than those of gravity. Thus, while the effect of gravity on arterial  $P_{O_2}$  is barely measurable,  $V'A/Q'$  mismatching based on nongravitational influences in many diseases leads to profound gas exchange disturbances. However, the presence of gravity must not be discounted in several disease states. Emphysema, and even the normal ageing process, often causes tissue breakdown in the apical lung regions, probably because, as in the Slinky analogy, the alveolar wall stresses are largest there. When mechanical failure occurs, it is most likely to happen in the regions of greatest stress and as a result the alveolar wall breakdown so typical of emphysema, and to a much lesser extent normal ageing, is often exaggerated in the apices. An important gravitational influence occurs in patients in intensive care with severe lung disease. In any body position, both blood flow and alveolar fluid collection tend to be concentrated in dependent regions (e.g. posteriorly in the supine patient). Those regions with high blood flow

may also have little or no ventilation if their alveoli are filled with fluid and cell debris. The blood flowing through such regions can therefore pick up little or no O<sub>2</sub>, and hypoxaemia may be severe. This has led some intensive care staff to rotate their patients from supine to lateral to prone and back; the argument being that the gravitational influences on blood flow are essentially instantaneous, while those on alveolar fluid collection may take hours to respond to body positional changes. Thus, for a time after rotating a patient, the dependent region may enjoy high flow but not yet be fluid filled, and thus still be well ventilated. Gas exchange is therefore enhanced, and arterial hypoxaemia is mitigated. Such behaviour may also explain positional influences on gas exchange in patients with unilateral lung disease such as pneumonia, effusion, or atelectasis. FURTHER READING Crystal R, West JB (1997). The lung: scientific foundations. Raven Press, New York. Weibel ER (1963). Morphometry of the human lung. Springer-Verlag, Berlin. Weibel ER (1984). The pathway for oxygen: structure and function in the mammalian respiratory system. Harvard University Press, Cambridge, MA. West JB (2004). Respiratory physiology, the essentials, 7th edition. Williams & Wilkins, Baltimore, MD.

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