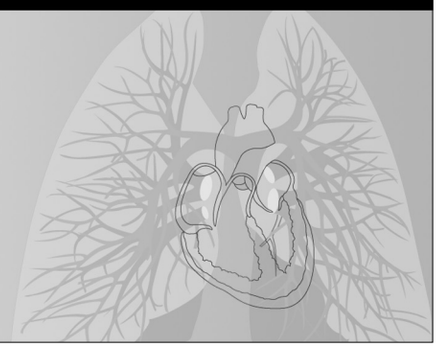
SECTION 1
Physiology



CHAPTER 1
Structure–function relationships: the pathophysiology of airflow obstruction

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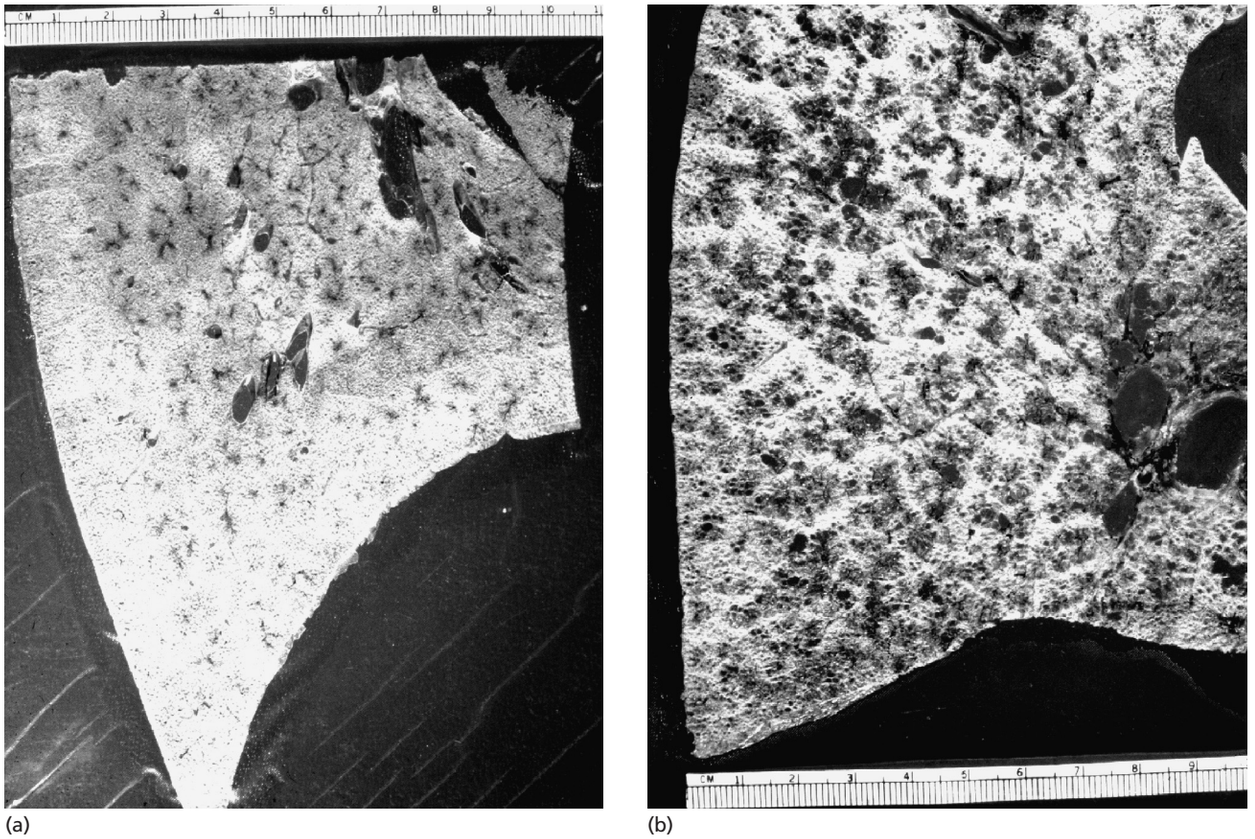
A decrease in maximal expiratory flow rates is the cardinal physiological abnormality associated with chronic obstructive pulmonary disease (COPD). Expiratory flow obstruction is deemed to be so important that the presence and severity of COPD is commonly defined in terms of the forced expiratory pressure in 1 second (FEV_1) and of the ratio of the FEV_1 to the forced vital capacity (*FVC*) [1]. The morphological features thought responsible for expiratory airflow obstruction also play a prominent part in the causation of other physiological derangements in COPD, such as hyperinflation and uneven ventilation. These various functional abnormalities largely reflect the passive mechanical properties of the lung, namely the elastic behaviour of lung parenchyma and airways, and the flow-restrictive characteristics of the bronchial tree. The pathological lesions found in the lungs of COPD patients have been described in some detail, and they can be broadly classified into those that principally affect lung elastic recoil (emphysema) and others that primarily affect the flow-restrictive properties of the bronchi and bronchioles (airways disease). Ideally, an expert pathologist would be able to estimate accurately the degree of airflow obstruction from a comprehensive quantitative assessment of the diseased lung. This can be accomplished in rather broad terms, but the state-of-the-art falls well short of the ideal. The physiologist's assessment of disease severity in the individual case may be markedly discrepant from that of the pathologist. These failures reflect our incomplete understanding of basic pathophysiology in COPD, as well as the formidable methodological problems in studying an organ so structurally and functionally complex as the lung. This chapter describes some of the interrelationships of pathology with physiology in COPD.

Pathology

Emphysema

Patients with symptomatic COPD nearly always have some emphysematous involvement of their lungs, although the extent may vary widely among patients who have the same degree of spirometric impairment. Patients are sometimes labelled with a clinical diagnosis of 'emphysema', but this usage is discouraged because emphysema has a stricter, pathological definition. An expert committee has defined emphysema as 'a condition characterized by abnormal enlargement of the airspaces distal to the terminal bronchiole, accompanied by destruction of their walls, and without obvious fibrosis' [1]. Enlargement of the parenchymal airspaces within the gas exchange region of the lung (alveolus, alveolar duct and respiratory bronchiole) is the seminal feature of emphysema (Fig. 1.1). Airspace enlargement may be caused by actual departitioning and fenestration of the alveolar walls or by a simpler structural rearrangement of the normal acinus. Airspace enlargement is a normal feature of the ageing lung ('senile emphysema'), and it may also be observed in diseases such as interstitial fibrosis. Focal areas of fibrosis may be found in many lungs that are judged to have predominantly emphysema, particularly of the centriacinar subtype. Consequently, it may be difficult to ascertain the presence of mild grades of emphysema in the lungs of older patients, and in some instances there may be confusion as to whether airspace enlargement should be attributed to emphysema or to a separate disease process.

Pathologists recognize two principal subtypes of emphysema. Centriacinar, or centrilobular, emphysema is characterized grossly by discrete, enlarged airspaces, usually measuring 1–10 mm in diameter, which tend to be most prominent in the upper lobes. Microscopically, these



(a) (b)

Figure 1.1 Macroscopic sections of inflation-fixed lungs comparing a normal subject (a) with a COPD patient having moderately severe emphysema (b). The emphysema has both centriacinar and panacinar features.

lesions may be seen in the proximal parts of the respiratory bronchiole, which is the partially alveolated airway immediately distal to the terminal bronchiole. Alveolar structures in the more distal acinus are usually well preserved, although very large centriacinar emphysema lesions may obliterate much of the acinus. Focal areas of inflammation, fibrosis and carbonaceous pigment are commonly present in adjacent alveolar and bronchiolar walls.

As the name implies, panacinar, or panlobular, emphysema, more uniformly involves the entire acinus. Macroscopically, mild panacinar emphysema appears as a subtle diffuse enlargement of airspaces, which resembles the aged lung. With progression of the disease, single lesions coalesce to form airspaces measuring millimeters to centimeters in diameter; large bullae may form in severe cases. Microscopically, alveolar ducts are diffusely enlarged, and adjacent alveoli become effaced to the extent that individual units cannot be identified. Panacinar emphysema involves all regions of the lung, and some patients, particularly those with severe α_1-antitrypsin deficiency, may exhibit a basal predominance.

When lung sections are appropriately stained, a dense labyrinth of elastic fibres becomes visible within alveolar walls and around peripheral airways (Fig. 1.2). This intricate elastic fibre network helps maintain normal parenchymal structure and contributes importantly to the lung's distinctive elastic recoil properties. The prevailing theory is that emphysema develops from an elastase–antielastase imbalance causing damage to the elastic fibres within the lung parenchyma. Despite their presumed importance in the pathogenesis of emphysema, surprisingly little is known about the state of elastic fibres and other extracellular matrix components in severe human emphysema. Existing studies are mostly descriptive and such basic information as the elastin content of the emphysematous lung is not available.

Emphysema is an anatomical entity, so that estimates of prevalence and severity can be directly made only from specimens obtained by surgical resection or at autopsy. Because reliable estimates of emphysema severity require that specimens be fixed in a uniformly inflated state, whole lungs or lobes are generally more satisfactory than smaller lung samples. The most widely used and accepted method for estimating emphysema severity utilizes a standard panel

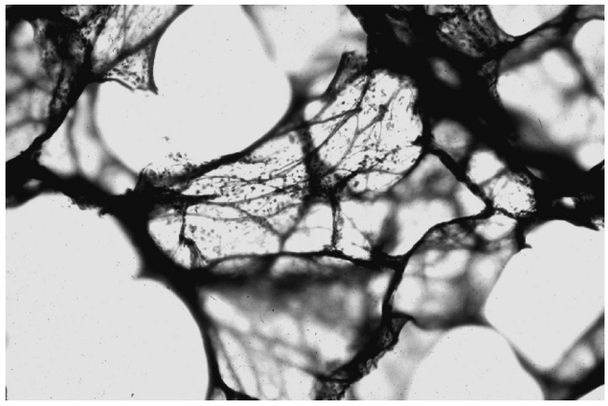


Figure 1.2 Thick histological section of normal human lung stained for elastic fibres. Elastic fibres appear as a lacy network of thin dark lines when an alveolar wall is viewed *en face*. Thicker elastic fibres surround the ostia connecting alveolar ducts with individual aveoli. Elastic fibres are major contributors to lung elastic recoil.

that depicts whole lung sections with increasing degrees of emphysema [2]. The lung section in question is subjectively scored by direct comparison against the panel. Determination of a mean linear intercept (average distance between alveolar walls) is the preferred method for evaluating emphysema severity from histological sections. This method has the advantage of being truly quantitative, but it is time and resource intensive and, because of sampling issues, it is limited in its capability for distinguishing mild emphysema from normal lung [3]. Milder forms of emphysema may be focal in their distribution, and can usually be best appreciated from visualization of whole-lung slices. Estimates of emphysema severity by the picture panel and the mean linear intercept methods are generally in good agreement, but for most purposes the picture panel method is considered the gold standard.

There is now good evidence that reliable estimates of emphysema severity may be made indirectly from computed tomography (CT). Studies to date have consistently shown a good correlation between regions of reduced lung tissue density found on CT scan and the presence of anatomical emphysema [4]. CT scans are highly specific, but they lack sensitivity in detecting very mild grades of emphysema. This is an evolving technology, with issues relating to sensitivity, specificity and standardization currently being addressed.

Airways disease

Much confusion attends the terminology associated with airways disease in COPD. The term 'chronic bronchitis' has been widely used but with a variety of meanings. Strictly speaking, 'chronic bronchitis' refers to an inflammatory condition involving the bronchi, which are the more central, larger and cartilage-containing airways. (The more peripheral airways without cartilage are termed bronchioles.) However, pathologists sometimes refer to bronchial mucous gland enlargement as 'chronic bronchitis'. To complete this rather illogical pattern, the term has also used to define a 'clinical disorder characterized by excessive mucus secretion in the bronchial tree, manifested by chronic or recurrent productive cough on most days for a minimum of 3 months per year for not less than 2 successive years' [5]. Experts arrived at this definition when excess mucus secretion was thought to have a central role in the development of airflow obstruction in COPD. This is no longer thought to be the case, but the definition persists to the bewilderment of several generations of medical students and residents. To avoid this confusion, all pathological changes within the bronchial tree that have been implicated in the pathophysiology of COPD will be called simply 'airways disease'. For reasons that will later become evident, it is appropriate to distinguish pathological changes that primarily involve the central bronchi from those found in the peripheral bronchioles.

Central airways disease

Mucus lines the airway lumens of the bronchial tree and serves an important role in host defence against the environment. Mucous glands, containing both mucous and serous cells, are found between the epithelial basement membrane and the cartilage plates of the central bronchial tree. Mucus is actively secreted into the bronchial lumen via specialized ducts. Modest enlargement of the bronchial mucous glands is found in the lungs of many patients with COPD but not all. Bronchial mucous gland enlargement correlates with cough and excess sputum production [6]. The Reid Index was the first described method for quantifying the degree of mucous gland enlargement [7]. In this technique, the width of the mucous gland is compared with the width of the bronchial wall between the basal lamina and the perichondrium. This method has been largely supplanted by better methods which quantify area proportions. The volume of bronchial mucous gland may increase by 50–100% in selected cases of severe COPD (Fig. 1.3).

In addition to the mucous glands, mucus-secreting goblet cells are found in airway epithelium at all levels of the conducting airways. The population of epithelial goblet cells may expand in the larger airways of COPD patients, but existing studies are mostly descriptive. Epithelial metaplasia and loss of cilia have also been described. It is not clear whether the proportions of smooth muscle and cartilage are abnormal in lungs of COPD patients. COPD is commonly associated with a low-grade inflammatory response within the epithelium and submucosa of the more central

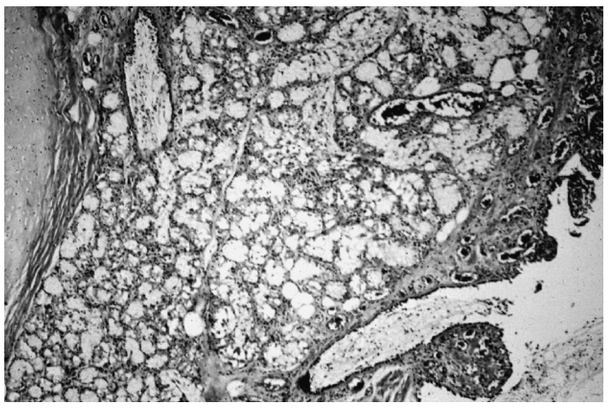


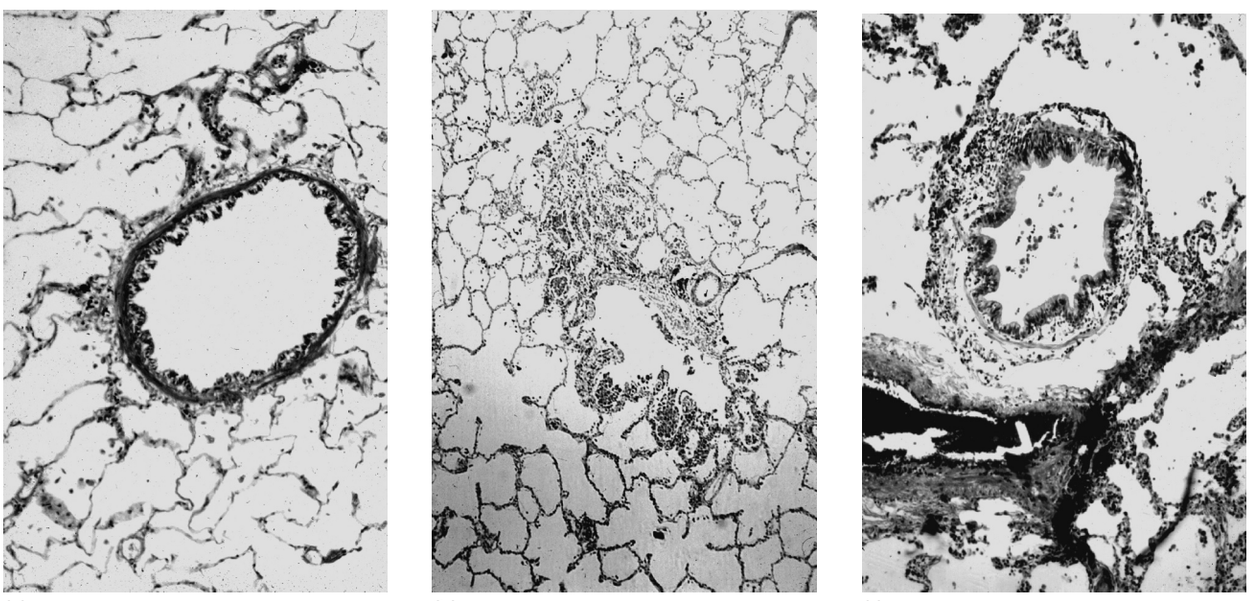
Figure 1.3 Histological section of a cartilaginous bronchus from a COPD patient with chronic cough and sputum production shows marked mucous gland enlargement. Mucous glands normally occupy but a small part of the area between cartilage and epithelium. A low-grade inflammatory reaction commonly accompanies mucous gland enlargement.

bronchi. Neutrophils, macrophages and $CD8^+$ T lymphocytes are the predominant inflammatory cells [8].

Peripheral airways disease

The pathological changes seen in the peripheral airways of COPD patients are multiple and relatively non-specific (Fig. 1.4). The earliest abnormalities seen in lungs from young smokers are focal collections of brown-pigmented macrophages in the proximal respiratory bronchioles [9]. In older patients with established COPD, the walls of membranous bronchioles frequently contain a low-grade inflammatory response that includes scattered neutrophils, macrophages and lymphocytes [10]. Additional abnormalities include fibrosis, goblet cell and squamous cell metaplasia of the lining epithelium, smooth muscle enlargement and scattered aggregations of mucus within the lumen. Most of this pathology can probably be directly attributed to the toxic effects of cigarette smoke, but peripheral airways in the lungs of elderly lifelong non-smokers may exhibit some of the same abnormalities [11].

Measurements in lungs obtained at surgery and at autopsy indicate that the internal calibre of fully distended peripheral bronchioles is smaller in COPD patients compared with normal subjects [11,12]. In addition, the walls of bronchioles from COPD patients are abnormally thickened, with the increased width being caused by epithelial, smooth muscle and connective tissue elements [13]. Abnormally thickened airway walls may take on added functional significance at smaller lung volumes, because the peripheral airways shorten and narrow as the lung deflates. Figure 1.5 illustrates this point. In the example shown, the abnormal airway has a wall that is twice the



(a) (b) (c)

Figure 1.4 Normal terminal bronchiole from a human lung is a thin-walled structure with an internal diameter of approximately 0.5 mm (a). Section through the junction of a membranous and respiratory bronchiole from the lung of a young adult shows the typical inflammatory lesion caused by cigarette smoking (b). Clusters of brown-pigmented macrophages are visible in the respiratory bronchiole and a few mixed inflammatory cells are present within the walls of the membranous bronchiole. In patients with established COPD, membranous bronchioles may exhibit thickened walls and narrowed distorted lumens (c).

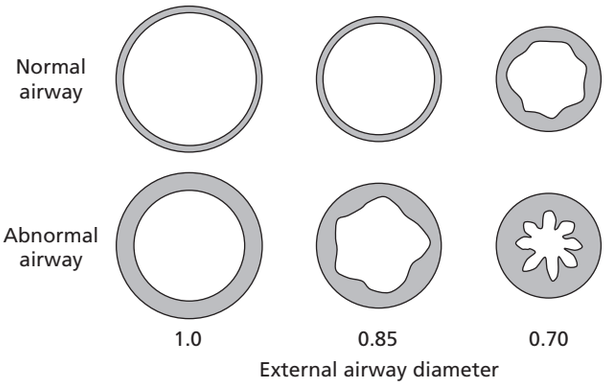


Figure 1.5 External airway diameter decreases as lung volume becomes smaller. Because the volume of the airway wall remains constant, the wall becomes thicker at smaller lung volumes, with a disproportionate reduction in the calibre of the lumen. At very small lung volumes, longitudinal folds may develop along the inner wall of the airway. Abnormally thick airway walls, as occurs in COPD, may exaggerate this effect.

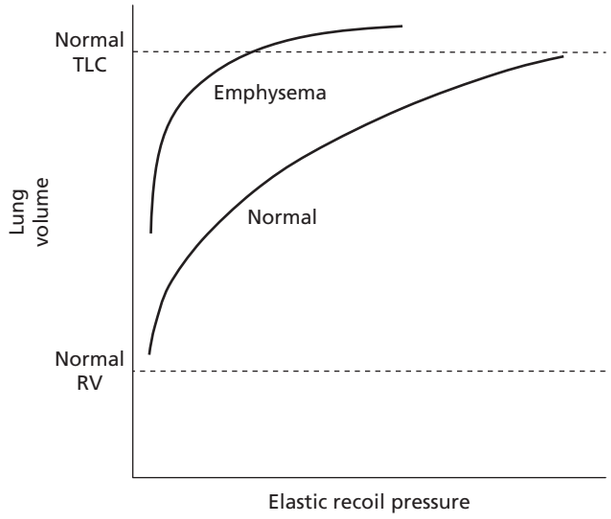


Figure 1.6 Lung volume as a function of lung elastic recoil pressure in a normal subject and in a COPD patient with extensive emphysema. At any particular lung volume, lung elastic recoil pressure is reduced with emphysema. In addition, the pressure–volume curve in the emphysema patient exhibits greater concavity towards the pressure axis. RV, residual volume; TLC, total lung capacity.

normal thickness. For the same change in external diameter, the lumen of the abnormal airway wall narrows to a far greater extent because the constant volume of excess tissue tends to bulge inward. This effect is greatly magnified at very small lung volumes, where the development of longitudinal folds along the inner surface may predispose to complete airway closure.

The accurate assessment of diverse pathological features that are widely distributed among tens of thousands of individual airways presents a formidable problem. Standardized scoring systems and direct quantitative approaches that measure the dimensions and volume components of the airways have largely supplanted earlier descriptive studies [11,12,14]. However carefully they are performed, assessments of airways in fixed tissues may poorly reflect their functional behaviour during the respiratory cycle. There have been efforts to image airways with CT and ultrasound during life [15,16]. These methods are interesting and promising, but they have yet to be fully validated. The major issue is whether they are capable of adequately resolving the dimensions of the smaller airways.

Physiological abnormalities

Lung elastic recoil

Lung elastic recoil refers to the lung's intrinsic tendency to deflate after it has been inflated. This relationship is commonly expressed by plotting lung volume as a function of transpulmonary pressure under the condition of no airflow (Fig. 1.6). Transpulmonary pressure is defined as the pressure differential between the inside and the outside of the pleura. Pressure in the pleural space may be roughly estimated from a balloon catheter placed in the mid-oesophagus. In normal young adults, transpulmonary pressure at total lung capacity (TLC) is typically in excess of 35 cm H_2O and at functional residual capacity (FRC) is approximately 5 cm H_2O. Lung elastic recoil is sometimes defined in terms of compliance, defined as the change in lung volume relative to the change in pressure. The pressure–volume relationship is curvilinear through its entirety, and as a result, compliance has a unique value at each lung volume. There has been some success in fitting empirical mathematical models to the pressure–volume curve so that the entire relationship can be described by estimation of one or two parameters [17,18]. For most purposes lung elastic recoil can be adequately described in terms of the transpulmonary pressure at some specified lung volumes, TLC and FRC being most commonly used.

Loss of lung elastic recoil is one of the distinguishing features of ageing. This occurs in a manner so predictable that age can be estimated with fair accuracy from the pressure–volume characteristics of a postmortem lung [17]. Age-related losses in lung elasticity probably explain much of the decrease in spirometric function that occurs with advancing age.

Lung elastic recoil may be divided into two components: one resulting from tissue elasticity and a second attributable

to the air–liquid interface at the alveolar surface. Tissue elasticity arises from the rich network of elastic fibres within lung parenchyma, from other components of the extracellular matrix, and from the geometrical arrangements of these elements. Isolated elastic fibres behave much like rubber bands, snapping back to their original position upon being stretched to twice their resting length. Alveolar structures are sufficiently small that surface tension at the air–liquid interface creates significant pressure within the alveolar spaces, even in the presence of the surface tension-lowering substance, surfactant. This relationship is defined by the law of Laplace, which states that the pressure within a wetted sphere is proportional to the tension within the lining liquid film and inversely proportional to the radius of curvature. Comparing pressure–volume curves from air- and fluid-filled lungs delineates the contribution of tissue elements and of surface tension. Both make substantial contributions in the human lung. Hence, damage to matrix elements and loss of alveolar surface area would both be expected to reduce lung elastic recoil.

Because damage to elastic fibres and loss of alveolar surface area are the characteristic pathological features of emphysema, a decrease in lung elastic recoil would be anticipated. This prediction has been fully confirmed and Figure 1.5 illustrates the typical abnormality. Compared with normal, the severely emphysematous lung exhibits a substantial loss in elastic recoil pressure at all lung volumes. In addition, the pressure–volume curve in severe emphysema exhibits a shape change, being somewhat more convex with respect to the pressure axis. These altered lung elastic properties might be viewed as the primary functional defect associated with human emphysema.

Airflow resistance

The human bronchial tree is a complex structure. Starting with the trachea, conducting airways branch in an irregularly dichotomous pattern. Different pathways from trachea to terminal membranous bronchiole may encompass as few as 10 generations or as many as 25. Further branching occurs within the partly alveolated respiratory bronchioles distal to the terminal bronchiole. The internal diameter of the adult trachea is approximately 2 cm. Airway calibre decreases with each succeeding generation to a miniscule 0.5 mm at the level of the terminal bronchiole. Because there are approximately 50 000 terminal bronchioles in each human lung, total cross-sectional area at this level of the bronchial tree exceeds that of the trachea by about two orders of magnitude. Hence, the velocity of airflow during the breathing cycle is substantially larger in the central airways compared with the peripheral airways.

A pressure differential is necessary to generate airflow through a cylinder. The ratio of the longitudinal pressure difference to the flow rate defines airflow resistance. The magnitude of airflow resistance varies with the flow profile (laminar versus non-laminar), the physical properties of the gas and the dimensions of the cylinder. The many airways comprising the bronchial tree can be viewed as resistive elements existing in series and in parallel.

As is true for lung parenchyma, airways exhibit intrinsic elastic behaviour which allows them to widen or narrow in response to traction and pressure differentials. Because of the cartilaginous rings within their walls, proximal bronchi are relatively rigid structures. However, the membranous posterior portion is easily deformed, and it will bow inward to occlude the airway lumen when subjected to large compressive pressures. Peripheral bronchioles have little inherent rigidity. The relatively thin, cartilage-free walls of these airways are embedded within lung parenchyma, and they depend upon the tethering effect from alveolar wall attachments to maintain patent lumens. The outward tension exerted by alveolar walls is a function of lung volume; the bigger the volume, the larger the lung elastic recoil, and the greater the tension within each alveolar attachment. If the lung were to exhibit perfect isotropy, a 50% reduction in lung volume would be associated with a 21% reduction in airway calibre.

Assessment of airflow resistance requires simultaneous measurements of airflow at the mouth and of pressure differential between the mouth and the alveolus. Alveolar pressures can be estimated either with an oesophageal balloon or by a plethysmographic method. Figure 1.7 compares

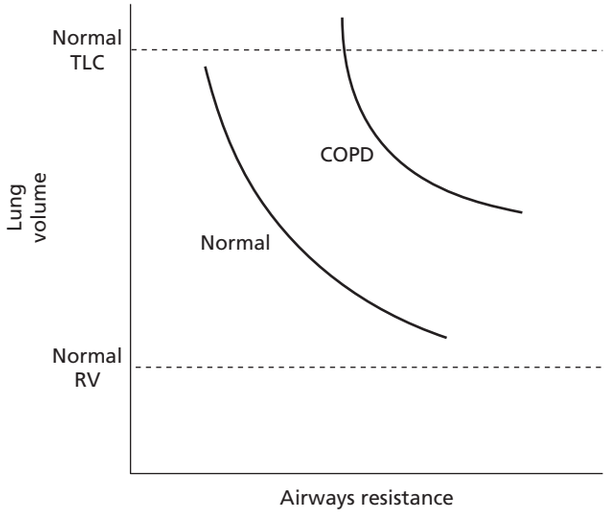


Figure 1.7 Lung volume as a function of airways resistance in a normal subject and in a COPD patient. In both patients airways resistance increases as lung volume becomes smaller. At any given lung volume, airways resistance is considerably larger in the COPD patient. RV, residual volume; TLC, total lung capacity.

typical airflow resistance as a function of lung volume in a normal subject with that in a COPD patient with emphysematous lungs. There is a strong volume dependence of airflow resistance in both subjects, this reflecting the decrease in lung elastic recoil and consequent reduction in airway calibre at smaller lung volumes. Airflow resistance is substantially higher at comparable lung volumes in the patient with COPD, and this might be attributed to two distinct mechanisms. At the same lung volumes, lung elastic recoil would be less in the emphysematous lungs, with the expectation that airways would be narrower and airflow resistance would be higher. It is possible to negate this effect by comparing airflow resistance in different lungs at the same lung elastic recoil pressures. Under these conditions, airflow resistance is still substantially higher in COPD compared with normal. This strongly suggests structural and functional abnormalities inherent to the conducting airways cause increased airflow resistance in COPD.

The dominant site of airflow resistance within the pulmonary airways is not intuitively obvious. The bronchial tree is a complex structure and pathological changes have been described at all levels in lungs from patients with COPD. The peripheral bronchioles are much smaller than the proximal bronchi, but there are a great many of them. Total cross-sectional area at the level of the terminal bronchiole is larger than the trachea by orders of magnitude. However, this tells us little about the relative flow-resistive properties at the two levels, because area changes as the square of airway radius while resistance changes as the fourth power or higher.

Studies with a retrograde catheter in excised animal and human lungs provide an invaluable clue to the site and nature of increased airflow resistance in COPD [19,20]. The catheter was placed at a site in the bronchial tree where airflow resistance in airways less than 2 mm diameter could be partitioned from resistance in airways with a diameter of greater than 2 mm. The first studies were performed in normal dogs and they yielded results that at the time were considered rather surprising [19]. The peripheral component accounted for only approximately 10% of total airflow resistance, a value much smaller than had been suggested by earlier studies.

Retrograde catheter studies of central and peripheral airflow resistance were subsequently made in postmortem lungs from subjects with and without COPD [20]. As was the case in dog lungs, the peripheral component of total airflow resistance in normal human lungs appeared quite low, representing only 10–20% of the total. In lungs from COPD patients, the central component of airflow resistance was only slightly increased from that in normal lungs. However, the peripheral component was increased by factor of between 10 and 20. These observations added enormously to our understanding of the pathophysiology of COPD, because they indicated that it was disease in the distal airways and not the large bronchi that was principally responsible for increased airflow resistance in COPD.

The partitioning of airflow resistance in normal and diseased human lungs also led to a novel idea about the natural history of COPD, which in turn spawned a large and mostly futile research effort. The retrograde catheter studies indicated peripheral airflow resistance was negligible in normal lungs, but predominant in severe COPD. Therefore, early stages of the disease might be associated with pathological changes in the peripheral airways that had minimal effect on standard tests of lung function, such as the FEV_1. It was further reasoned that these early changes might better be detected with more sensitive, non-standard tests. Considerable effort was expended in developing and evaluating newer, so-called 'tests of small airways disease', including the frequency dependence of dynamic lung compliance, the single breath nitrogen washout test, and spirometry with exotic gas mixtures. These tests have long been abandoned, because a variety of epidemiological and pathological–physiological correlative studies indicated that these newer, specialized tests offered little advantage over the FEV_1 in detecting the earliest stages of COPD [21–24].

These newer tests failed in part because they were based on a faulty rationale. Studies by other investigators indicated that the original retrograde catheter studies were subject to methodological errors that led to a systematic underestimate of peripheral airflow resistance in both normal and COPD lungs [25,26]. Repeat measurements in human lungs indicated that the peripheral component represents approximately 90% of total airflow resistance in the normal lung [27]. Additionally, studies in normal postmortem lungs demonstrated a remarkably good correlation between total airflow resistance and the diameter of the peripheral airways, but not with the diameter of the proximal airways [28].

These findings have important implications regarding our understanding of COPD. They lend strong support to the concept that the peripheral airways, and not the central airways, are principally responsible for the increased airflow resistance in COPD. If the peripheral airways determine levels of ventilatory function in the normal lung, it logically follows that relatively minor pathological changes in those same airways take on added functional significance in disease states.

Maximal expiratory airflow limitation

Spirometry is recommended as the single best test for the diagnosis of COPD. During this procedure maximal expiratory airflow is measured as a function of time, and the result is graphically displayed as either a volume–time or flow–volume plot. The two plots contain identical

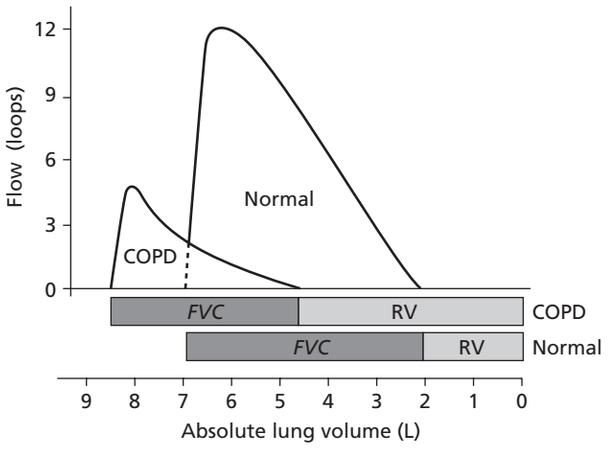


Figure 1.8 Expiratory flow–volume loops as a function of absolute lung volume in a normal subject and in a patient with COPD. This figure illustrates the cardinal functional abnormalities associated with COPD, expiratory airflow limitation and hyperinflation. *FVC*, forced vital capacity; RV, residual volume.

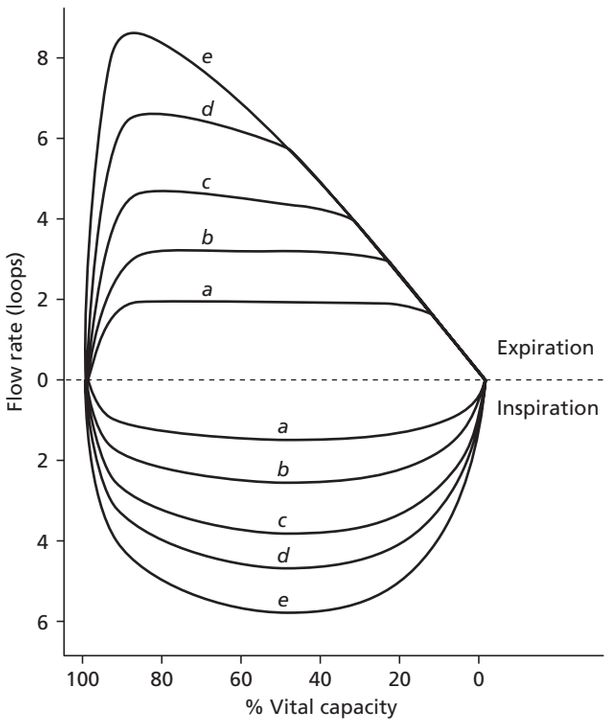


Figure 1.9 A normal subject performed a series of full inspiratory and expiratory manoeuvres with graded effort (*a*–*e*). On the expiratory limbs, flow rates are independent of effort at smaller lung volumes. This phenomenon, described as 'flow limitation' or 'effort-independence', is not seen with inspiratory manoeuvres.

information. The most common parameters extracted from the spirogram are the FEV_1 and the *FVC*. The expiratory flow rate between 200 and 1200 mL of the *FVC*, the mid-expiratory forced expiratory flow rate between 25% and 75% of the *FVC*, and other less frequently used spirometric parameters contain little additional diagnostic information and have fallen out of favour. A decrease in the FEV_1, best expressed as the percentage of predicted, and a decrease in the ratio of the FEV_1 to the *FVC* (FEV_1/FVC) are the hallmark spirometric abnormalities of COPD.

Figure 1.8 shows representative flow–volume curves from a normal subject and from a patient with COPD. At any given fraction of *VC*, maximal expiratory flow rates are smaller in the COPD patient. In this example, flow rates are shown as a function of absolute lung volume to illustrate another of the cardinal physiological abnormalities in COPD. The COPD patient exhibits hyperinflation in that both the TLC and residual volume (RV) are shifted to larger lung volumes.

Forced expiratory flow–volume curves exhibit a phenomenon that is termed airflow limitation. The principle can be demonstrated by having a normal subject perform a series of full inspiratory and expiratory breathing manoeuvres between RV and TLC, each with a different strength of effort. Figure 1.9 depicts these graded efforts (*a* increasing through *e*) as a family of flow–volume loops. Greater effort during the inspiratory phase yields larger flow rates, and these increases are roughly proportional at all lung volumes. On the expiratory cycle, greater effort also generates larger flow rates, but only at the higher lung volumes. At intermediate and low lung volumes, airflow increases with added effort, but only up to a certain point. At that point the tracing superimposes those from other individual efforts. Over the lower two-thirds of the vital capacity a ceiling becomes evident, beyond which airflow does not increase further however great the expiratory effort. Expiratory flow rates at these lung volumes are sometimes described as being 'flow limited' or 'effort independent'.

The principle of flow limitation can be demonstrated in somewhat better detail from what are called isovolume pressure–flow diagrams (Fig. 1.10). Inspiratory and expiratory flow are plotted as a function of alveolar pressure at specified lung volumes. The pressure differential between the mouth and the alveolar space, or driving pressure, generates airflow though the bronchial tree. Alveolar pressure is negative with respect to the mouth during inspiration and positive with expiration. During inspiration, airflow remains linear with driving pressure at each of the indicated lung volumes, meaning that airflow resistance remains nearly constant. Hence, inspiratory flow is largely limited by the magnitude of the applied pressure, which is largely a function of respiratory muscle strength. Differences in

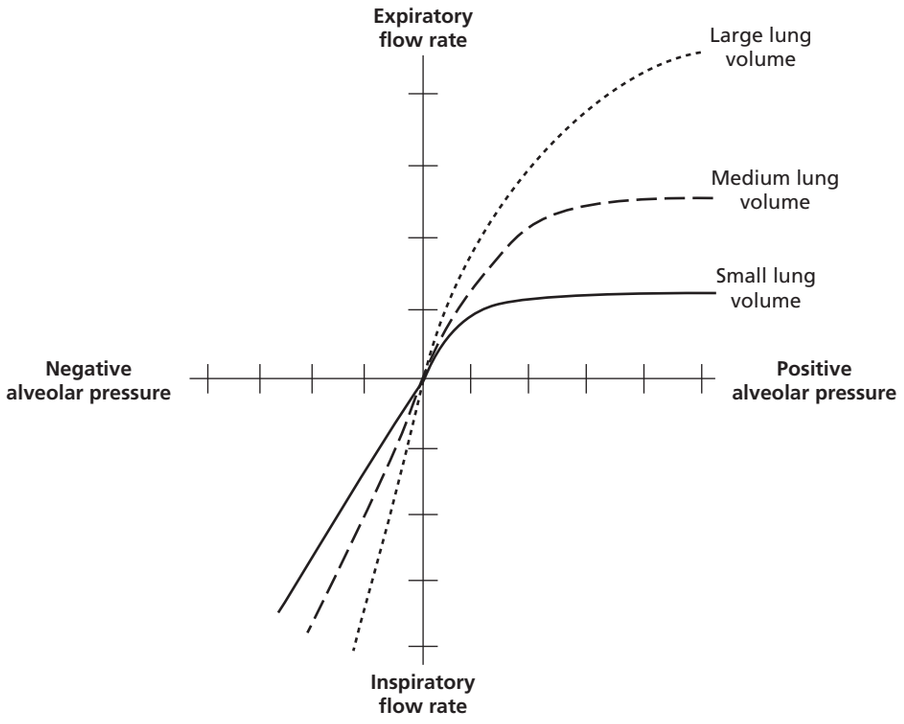


Figure 1.10 Relationship of inspiratory and expiratory airflow rates to alveolar pressure at various lung volumes. With inspiration, flow increases proportionally to alveolar pressure. With expiration, flow increases with alveolar pressure only to a certain point, beyond which flow remains constant despite greater alveolar pressures. This effect, flow limitation, is most pronounced at smaller lung volumes.

the slopes of the pressure–flow relationships at the three different lung volumes indicate that airflow resistance becomes greater as lung volumes become smaller.

The patterns obtained during expiration are qualitatively different in that relationships between the pressure differential and airflow are curvilinear rather than linear. This is most obvious at smaller lung volumes where a fairly sharp inflection occurs at a relatively low driving pressure. Beyond this inflection, the relationship assumes a plateau shape, meaning that airflow is independent of changes in driving pressure. In other words, greater expiratory effort creates greater airflow resistance with no increase in airflow. Limitations to expiratory airflow are set by the mechanical properties of lung parenchyma and bronchial tree.

The relevance of expiratory airflow limitation to clinical disability can be appreciated by comparing flow–volume loops from a COPD patient with that of a normal subject. Figure 1.11 shows inspiratory and expiratory flow–volume loops during tidal breathing at rest and with maximal effort in the two subjects. Note that the normal subject has enormous reserve and from the resting state is able to increase minute ventilation by a large factor in response to increased metabolic demands. Consequently, ventilation is not a limiting factor, even with very vigorous exercise. In contrast, maximal inspiratory and expiratory flow rates are much smaller in the patient with COPD, expiration typically being more severely affected than inspiration. Most importantly, a large portion of the expiratory flow–volume loop

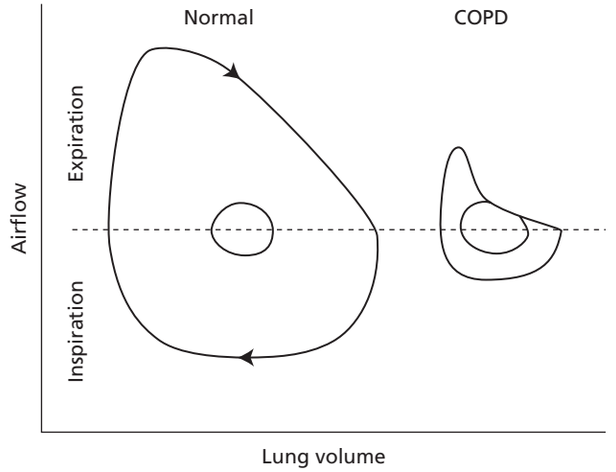


Figure 1.11 Inspiratory and expiratory flow–volume loops in a normal subject and in a patient with severe COPD. The outer loops represent maximal efforts and the loops represent tidal breathing. In the patient with COPD, expiration is flow limited even during a tidal breath.

obtained during tidal expiration superimposes that from a forced expiration. Severe COPD patients exhibit flow limitation even while meeting the minimal ventilatory requirements of the resting state. These patients have only limited capability for increasing minute ventilation in response to exercise. Their only effective strategy for increasing minute

ventilation is to shift tidal breathing to larger lung volumes where higher expiratory flow rates can be achieved. Clinical studies have shown that hyperinflation is a common response to increased workload in COPD patients [29]. Unfortunately, this compensatory mechanism comes with a price, because the lung and the thoracic cage both become stiffer at larger volumes. This increases the elastic workload of the respiratory muscles and is an important component in generating the sensation of breathlessness.

Mechanism of expiratory airflow limitation

Models of varying complexity have been used to analyse the physical behaviour of the lung in an effort to explain flow limitation during forced expiratory manoeuvres. A relatively simple model is described that provides some insight into this mechanism. The interested reader is referred elsewhere for more detailed and rigorous approaches to the subject [30–32].

The model shown in Figure 1.12 includes an expandable balloon to represent lung parenchyma. The balloon is contained within a box that depicts the thoracic cage. The space between the box and the balloon may be viewed as the pleural space. An airway with semi-rigid walls connects the balloon to the exterior. Up or down movement of the piston, representing the function of respiratory muscles, activates the model by altering intrapleural pressure (Ppl). The centrally directed arrows on the interior of the balloon symbolize lung elastic recoil.

Figure 1.12(a) shows the model at a fixed volume with no airflow. Under these static conditions, there is no gradient along the length of the airway and alveolar pressure (Palv) is equal to the reference pressure at the airway opening (Pao). The intrapleural pressure required to keep the lung statically inflated (arbitrarily chosen to be –10 cm H_2O in this example) is equal in magnitude but opposite in sign to the lung elastic recoil pressure (Pel). Hence, Palv is the algebraic sum of Ppl and Pel.

Downward motion of the piston creates a more negative Ppl. Palv now becomes negative with respect to Pao and air flows into the lung. On expiration, muscles relax and the lung typically contracts passively because of its inherent elastic recoil. As Ppl becomes less negative (–10 cm H_2O increasing to –5 cm H_2O), Palv becomes positive with respect to Pao and the lung exhales air (Fig. 1.12b). During the normal tidal breathing cycle, Ppl fluctuates by only a few centimetres H_2O and it remains negative even during expiration. As a result, pressure at each point within the conducting airway remains positive with respect to Ppl during the entire inspiratory and expiratory cycle. Consequently, an outwardly directed transmural pressure gradient expands the airway along its entire length, an effect that is greater during inspiration.

However, a forced expiratory effort creates a strongly positive Ppl that reverses the usual transmural pressure gradient along a segment of the airway. Figure 1.12(c) illustrates these pressure relationships during a submaximal forced expiration. Respiratory muscles generate sufficient force to increase Ppl to +10 cm H_2O. From the algebraic sum of Ppl and Pel, Palv now becomes +20 cm H_2O. The alveolar driving pressure dissipates along the length of airway lumen and at some point becomes equal to Ppl so that the transmural pressure gradient is zero. This is sometimes described as the 'equal-pressure point' (EPP). The EPP has no fixed anatomical site. Direct measurements suggest that the EPP is located in the central cartilaginous airways during the early stages of the maximal expiratory manoeuvre, but then migrates peripherally at lower lung volumes. Downstream from the EPP, intraluminal pressures become negative with respect to Ppl, creating a compressive force on the airway. Because the airway is not a rigid tube, compressive pressures narrow the lumen to some degree, thereby increasing airflow resistance. The length of compressed airway is referred to as the 'flow-limiting segment'.

Figure 1.12(d) illustrates the same relationships but with a more forceful expiratory effort. In this example, Ppl increases to +20 cm H_2O and the alveolar driving pressure, Palv, now enlarges to +30 cm H_2O. Because of the higher Ppl, compressive transmural pressures downstream from the EPP are now twice as large as in Figure 1.12(c). This further narrows the airway lumen with a corresponding increase in airflow resistance. In other words, greater expiratory effort increases the pressure head between alveolus and airway opening, but it also increases flow resistance because of greater compression of the airway downstream from the EPP. The result is little net change in expiratory airflow. This type of feedback mechanism for limiting flow is sometimes referred to as a Starling resistor, of which there are examples in other organ systems. It bears emphasizing that these relationships are exceedingly complex when analysed from first principles and no physical law requires that changes in Palv and airflow resistance need be strictly proportional. However, empirical observations indicate that these changes are roughly proportional in most human subjects.

The illustrated model permits some insight into other factors that might influence the flow-limiting airway segment. It is intuitively evident that a less rigid airway would narrow to a greater extent in response to the same transmural compressive pressure differential. Other conditions being equal, excessively compliant central airways would fix maximal expiratory airflow at a lower level. It is unclear from existing studies whether bronchial compliance is abnormal in well-defined patients with COPD.

Airflow resistance in more distal portions of the conducting airways may accentuate compressive effects on the

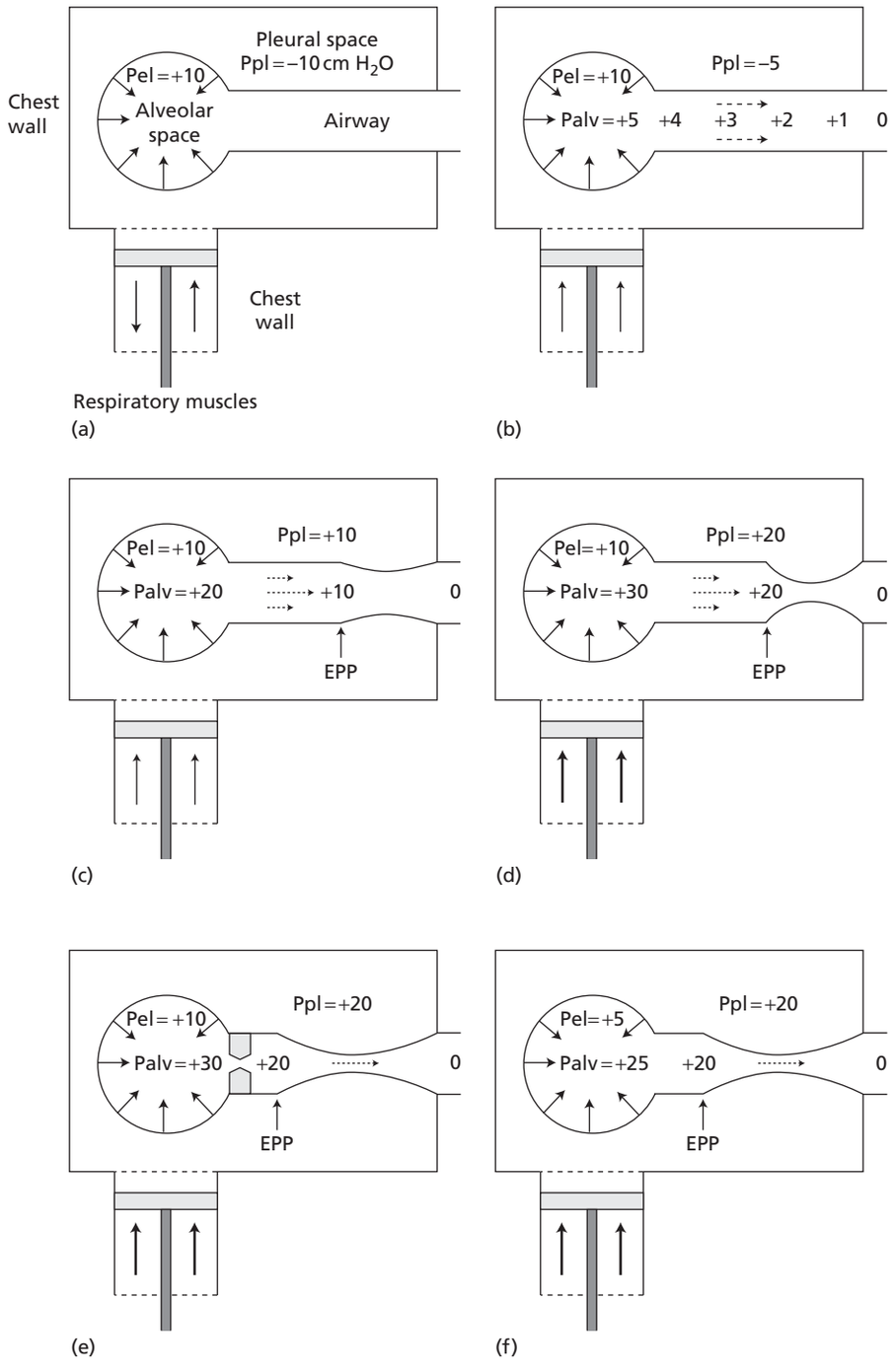


Figure 1.12 Model of expiratory flow limitation. See text for detailed explanation. (a) Description of static model. (b) Expiration during tidal breath. (c) Submaximal forced expiration. (d) Submaximal forced expiration but with greater effort than in (c). (e) Forced expiration with increase in peripheral airways resistance. (f) Forced expiration with decreased lung elastic recoil pressure. EPP, equal-pressure point; Palv, alveolar pressure; Pel, elastic recoil pressure; Ppl, intrapleural pressure.

more proximal flow-limiting airway segment. This is illustrated in Figure 1.12(e), which depicts partial obstruction in the most distal part of the airway. Peripheral airway narrowing may occur as a consequence of pathological features such as inflammation and excess mucus. As as result of the increase in peripheral airflow resistance, a greater portion of the driving pressure between alveolus and airway dissipates over the obstructed segment of airway. Hence, the EPP migrates distally and a longer segment of the more proximal airway is subjected to compressive pressures. Total airway resistance would increase and maximal expiratory airflow would be expected to decrease.

Loss of lung elastic recoil also has an impact on maximal expiratory airflow limitation. One mechanism relates to the effects of lung elastic recoil on the diameter of the intraparenchymal airways, which are not shown in the model. A decrease in lung elastic recoil at any specified lung volume will reduce airway calibre and increase peripheral airflow resistance. The effect on maximal expiratory airflow will be similar to that shown in Figure 1.12(e).

Another effect of elastic recoil on maximal airflow limitation is less intuitive. Note that an arbitrary value of 10 cm H_2O is assigned to Pel in Figure 1.12(a–e). Note also that when flow limitation becomes evident, as in Figure 1.12(d and e), the difference between Palv and the intra-airway pressure at the EPP has the same magnitude as Pel (10 cm H_2O). Viewed in this manner, lung elastic recoil effectively keeps airways open by opposing the high compressive pressures that develop in the pleural space during forced expiration. Figure 1.12(f) illustrates the effect of decreased lung elastic recoil on flow limitation. In this example, a Pel of 5 cm H_2O has been assigned to an 'emphysematous balloon'. With the same force exerted by respiratory muscles on the pleural space (Ppl = 20 cm H_2O), Palv now increases to only 25 cm H_2O instead of 30 cm H_2O. There is a corresponding decrease in the intra-airway pressure that opposes airway compression. Consequently, the EPP migrates distally, the compressed segment of airway becomes longer, with a corresponding decrease in maximal expiratory airflow.

Lung hyperinflation

A second characteristic and very important physiological abnormality in COPD is hyperinflation. This is variably defined as abnormally large TLC, FRC or RV. Lung volumes can be measured either by the washin or the washout of tracer gases, such as helium, or by plethysmography. Because tracer-gas methods require long equilibration times in the presence of severe COPD, plethysmography is the more accurate method. In clinical practice the diagnosis of COPD can usually be made from clinical and spirometric findings alone, but lung volume measurements may be useful in selected patients.

Figure 1.8 illustrates both the expiratory airflow abnormalities and the hyperinflation that are typical of COPD. As the FEV_1 and the *FVC* decrease, RV and TLC increase. Indices of hyperinflation, particularly the RV and RV/TLC, track closely with spirometric measures of expiratory airflow obstruction across a broad range of COPD severity [33]. This suggests that the functional and structural features that relate to expiratory airflow obstruction, namely loss of lung elastic recoil and increased peripheral airway resistance, are also responsible for an abnormally large RV.

RV is sometimes termed the 'volume of trapped air', a description that is probably apt. As described previously, lung volume, lung elastic recoil and peripheral airway resistance are intimately interrelated. As lung volume becomes smaller, elastic recoil decreases and the attendant loss of radial tension causes narrowing of the peripheral airways. At some point, resistance effectively becomes infinite and flow ceases. Several lines of indirect evidence suggest that peripheral airways in humans may actually close at lung volumes near RV, a phenomenon that has been directly observed in experimental animal lungs [34]. Calculations suggest that surface tension at the air–liquid interface on the epithelial surface of peripheral airways may be substantial as the lung volume nears RV, so that an intact surfactant system may be essential if the terminal bronchioles are to remain patent [35].

Structural correlates of expiratory airflow limitation

Expiratory airflow limitation is functionally related both to a loss of lung elastic recoil and to an increase in airflow resistance through the bronchial tree. Emphysema is presumed to be the morphological equivalent of abnormal lung elastic recoil, while a variety of pathological changes, particularly those in the peripheral airways, are thought to be responsible for increased airflow resistance through the bronchial tree. Consequently, there is the expectation that a detailed quantitative assessment of emphysema and airways disease in a lung from a COPD patient should allow a reasonably accurate prediction of spirometric function. Over the past several decades, numerous efforts to show such pathological and physiological correlations have yielded rather disappointing results.

Investigators have utilized several approaches when undertaking correlative structure–function studies, and each of these has certain advantages and limitations. Most commonly, investigators have compared lung tissue obtained at necropsy with function tests performed prior to death. Patients with severe disease tend to be heavily overrepresented in this type of study and the interval between the last pulmonary function test and death is variable. Tissue may also be acquired from patients undergoing lung resection surgery, which is usually performed for localized carcinomas. This approach has the major advantage of allowing detailed pulmonary function testing shortly prior to the scheduled surgery. It has the disadvantage of providing only a limited amount of tissue in most patients, with attendant problems in achieving uniform inflation and fixation. Also, potential surgical candidates must have sufficiently good lung function if they are to tolerate resection, which excludes most patients with severe COPD. Lung-volume-reduction surgery provides new opportunities for obtaining resected lung tissue from patients with severe disease, but the samples are relatively small and they

may be poorly representative of the remaining lung. Correlation studies have also been carried out in postmortem lungs. Tests of mechanical function performed in carefully selected postmortem lungs are reproducible, and forced expiratory flow rates obtained from such studies correspond quite closely with those obtained in living, age-matched adults [36]. The major disadvantage is in not knowing how severely postmortem changes might affect the results. Finally, CT imaging permits an accurate, indirect assessment of emphysema severity that can be compared against tests of function.

Efforts to show a correlation between emphysema severity and the FEV_1 have yielded inconsistent results [11,37–39]. Most published reports demonstrated either a relatively weak inverse relationship or one that was not statistically significant. Trivial degrees of emphysema may be associated with severe airflow obstruction in selected patients, while others may have normal or near-normal spirometry in the face of fairly advanced emphysema. In the largest series yet published, the Vancouver group of investigators found no statistically significant relationship between emphysema severity and the FEV_1 in 407 patients with mild-to-moderate COPD who were tested shortly before surgery for lung resection [38].

Efforts to show correlations between airflow obstruction and the severity of pathological changes in the conducting airways have fared no better. Numerous efforts to show correlations between expiratory airflow obstruction in COPD with mucous gland enlargement and other pathological features in the cartilaginous airways have been for the most part unsuccessful [40]. These results are perhaps not surprising in light of the retrograde catheter studies, which suggested that the principal pathological changes accounting for increased airflow resistance in COPD were to be found in the peripheral airways [20,27]. Those studies raised an expectation that careful assessments of peripheral airways disease, including features such as inflammation, fibrosis and smooth muscle enlargement, might show closer correlations with spirometric abnormalities. Early, small studies appeared to show such associations [10,41]. However, in the previously cited studies of 407 patients by the Vancouver group, no statistically significant relationship was found between the FEV_1 and total pathology score, or any of its components, for either the membranous or the respiratory bronchiole [38].

Thus, the largest and best available correlative studies indicate that the relationship of FEV_1 with either airway pathology or emphysema is at best tenuous. It bears emphasizing that most existing studies sampled only one part of the continuum between normal lung and severe COPD, and this provides a somewhat restricted view of the larger picture. For example, the Vancouver study included very few non-smokers and no patients with severe disease [38]. Many other studies have been restricted to patients with severe disease [37,39]. When a broader assessment is made in age-matched groups who may be presumed to have increasing levels of ventilatory dysfunction (never smokers, smokers without known COPD, and smokers with severe COPD), emphysema severity and multiple elements of airways disease were found to progress in parallel [11]. In addition, a wealth of circumstantial evidence from human studies and more direct evidence from experimental animal studies indicate that emphysema and some elements of airways disease are important morphological determinants of expiratory airflow obstruction. These considerations not withstanding, the ability to estimate the magnitude of ventilatory impairment in COPD from the most detailed pathological assessments is surprisingly poor. One can only speculate as to the reasons.

Ventilation distribution and gas exchange

COPD is characterized by progressive blood gas abnormalities. Mild hypoxaemia may be present in the early stages of COPD, and it usually progresses as the disease worsens. Hypercapnia may accompany more severe disease. Untreated hypoxaemia and hypercapnia can cause pulmonary hypertension and cor pulmonale, which contribute to the morbidity and mortality associated with this disease. The structural derangements and specific mechanisms responsible for gas exchange abnormalities in COPD are exceedingly complex and imperfectly understood.

Gas exchange within the lung is most efficient when the ratio of ventilation/perfusion ($\dot{V}/\dot{Q}$) remains close to unity within all lung regions. It is obvious that no gas exchange can occur if a ventilated zone receives no blood supply. A relative excess of ventilation is described as 'alveolar dead space', 'wasted ventilation' or a 'high $\dot{V}/\dot{Q}$ abnormality'. Such regions behave functionally as though some portion of the lung region received normal blood flow while the remainder received none. An increase in the dead space/tidal volume ratio (V_D/V_T) reflects lung zones with an abnormally high $\dot{V}/\dot{Q}$. V_D/V_T is usually 0.3–0.4 in normal subjects, but it may increase to as much as 0.7–0.8 in patients with severe COPD. In those patients the major portion of each inspired breath represents 'wasted ventilation'.

Alveolar regions that are underventilated in relation to their blood supply are described as low $\dot{V}/\dot{Q}$ zones. The proportion of cardiac output that passes through a completely unventilated lung region is termed the shunt fraction, and the admixture of shunted blood with other pulmonary venous blood is manifest as arterial hypoxaemia. A $\dot{V}/\dot{Q}$ region of less than 1 but greater than zero behaves as though some part of the region received normal ventilation and the remainder received none. Lung regions with low

$\dot{V}/\dot{Q}$ abnormalities are thought to be the principal cause of hypoxaemia in COPD.

Pathological states affecting either ventilation or perfusion homogeneity might in theory cause regional $\dot{V}/\dot{Q}$ to deviate from unity. Radioactive scanning and other techniques show that COPD is characterized by abnormal patterns involving both ventilation and perfusion. It is generally believed that pathological changes occur initially on the ventilation side and that abnormal perfusion patterns may partly result from compensatory flow regulation. Disease in the peripheral airways and alveolar spaces creates regions of both hyperventilation and hypoventilation. Hypoventilation causes localized hypoxia, which in turn stimulates a vasocontrictor response in the neighbouring arteries. The attendant reduction in blood flow re-establishes a regional $\dot{V}/\dot{Q}$ that is close to unity. Long periods of hypoxia may induce tissue remodelling in small pulmonary arteries, such as intimal fibrosis and smooth muscle hypertrophy, which lead to irreversible pulmonary hypertension. Because abnormalities in the pulmonary vascular bed may be regarded as secondary events, attention is directed to mechanisms by which abnormal ventilation patterns arise in COPD.

Ventilation is the process by which ambient air is transported to the alveolar spaces and resident air is removed to the environment. It is defined as the fractional turnover of inspired gas volume to resident gas volume for any given portion of the lung. Under normal resting conditions, each breath replaces approximately 10–15% of the resident gas volume. Gas is transported from the airway opening to the alveolar–capillary interface by convection and by diffusion. Transport within the proximal airways occurs by convection predominantly, whereas diffusion is more important within the alveolated gas-exchanging regions of the lung. Diffusion is not thought to be an important rate-limiting step for gas transport in the distal airways under normal conditions, but it may become so when diseases such as emphysema cause extensive anatomical rearrangements.

The compliance of a lung region and the change in transpleural pressure to which it is subjected determine ventilation. For a given change in transpleural pressure, a relatively more compliant lung region expands to a greater degree and receives more ventilation than does a less compliant region. An example is to be found in the normal human lung. As shown in Figure 1.6, the lung becomes progressively stiffer as it expands. As a result of gravity effects, a pleural pressure gradient develops from apex to base with apical pressures being more negative. Because the lung apex is subjected to a larger transpleural pressure, it is overinflated relative to the lung base. Consequently, the apex is less compliant and it receives a relatively smaller volume of each inspired breath than does the lung base. Non-homogeneous lung elastic behaviour brought about by any pathological condition could cause uneven ventilation by a similar mechanism.

Emphysema is a prototype of diseases that cause abnormal lung elasticity. Emphysema tends to be non-uniform in its distribution, both within a single region and between regions. Large emphysema lesions may reside immediately adjacent to apparently normal lung parenchyma. Because of differences in the shape of their respective pressure–volume characteristics, an emphysematous region might be either hyperventilated or hypoventilated relative to normal adjacent lung. This occurs because the pressure–volume curve of the emphysematous lung exhibits greater concavity towards the pressure axis (see Fig. 1.6). Consequently, it is overly compliant at low lung volumes but abnormally stiff at high lung volumes. If a discrete emphysema lesion were located at the lung apex so that it were subjected to a relatively large transpleural pressures, it would overexpand and be less compliant than surrounding normal lung. Therefore, this region would receive less ventilation with each tidal breath. By a parallel argument, the same emphysematous region might be abnormally compliant and overventilated if located at the lung base.

Existing evidence suggests that most emphysematous regions may be relatively underventilated, as shown in Figure 1.13 [42]. Other variables remaining constant, this should give rise to a low $\dot{V}/\dot{Q}$ zone. However, emphysematous regions also tend to be underperfused because a portion of the capillary bed has been lost. Thus, focal emphysematous regions could represent a broad range of $\dot{V}/\dot{Q}$ zones, both high and low, depending upon several critical variables.

Figure 1.13 illustrates another mechanism by which emphysema might cause uneven ventilation. In this example, the destructive change of early centriacinar emphysema is associated with a substantial enlargement of the respiratory bronchiole. Distal portions of the acinus remain largely intact. Enlargement of the proximal airway effectively increases the volume of 'dead space' ventilation to the more distal portions of that transport pathway. At end expiration, all gas-transport pathways contain resident gas. With the next inspiration, the 'dead-space' must be cleared before inspired air reaches the gas-exchanging region. With a larger 'dead space', a given volume of inspired air penetrates less deeply into the acinus. As a result, it is expected that the proximal emphysema lesion might be relatively overventilated while the more distal acinar regions might be underventilated.

Airways disease probably also contributes to $\dot{V}/\dot{Q}$ disturbances in the lungs of COPD patients, though little is known of specific mechanisms. Theoretical considerations suggest that at resting ventilation rates, severe airway narrowing or even complete closure would be necessary to substantially decrease ventilation to lung parenchyma

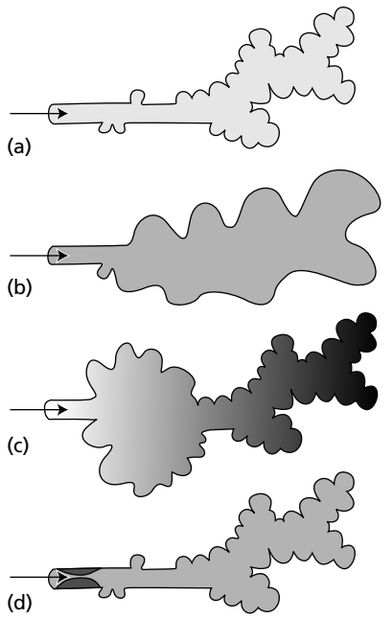


Figure 1.13 Postulated mechanisms for uneven ventilation in COPD. Dark shading indicates resident gas. Light shading represents inspired air. (a) Inspired breath is uniformly distributed in a normal lung unit. (b) Panacinar emphysema lesion is less compliant than normal lung and is less well ventilated, even though inspired air is uniformly distributed. (c) Centriacinar emphysema lesion increases 'dead space' so that distal portion of the unit is underventilated. (d) Obstruction of terminal bronchiole causes underventilation of distal alveolated structures.

subtended by a particular airway. Large plugs of mucus may sometimes occlude a proximal bronchus in patients with COPD, but the peripheral airways are probably more important as a cause of ventilation heterogeneity. Although never directly visualized, inflammatory exudate or excess mucus might well cause intermittent or complete obstruction of terminal bronchioles, resulting in an underventilated region (see Fig. 1.13). If the bronchiole were to remain occluded for an extended period, atelectasis might not occur because of ventilation via collateral channels.

Gas exchange is dependent on numerous other factors, including pulmonary blood flow distribution, neural control of breathing, chest wall mechanics, systemic haemodynamics, metabolic demands and respiratory muscle function. The final common expressions of disordered gas exchange in COPD, arterial hypoxaemia and hypercapnia represent a summation of multiple complex mechanisms.

Clinical and pathological subtypes of COPD

Older studies suggested that some patients with COPD could be fitted into so-called emphysematous and bronchitic subtypes, based upon certain distinguishing clinical, pathological and physiological criteria [43]. At one time this idea enjoyed widespread currency and the subject is still presented as established fact in some standard textbooks. As implied by their names, either predominant anatomical emphysema or predominant bronchitis (airways disease) was thought to provide the morphological basis for distinguishing clinical and physiological features. The patient with the emphysematous subtype of COPD was sometimes described as 'type A' or 'pink puffer', while the terms 'type B' or 'blue bloater' depicted the bronchitic subtype.

The typical emphysematous patient was described as a cachectic elderly individual who related a long history of progressive and unrelenting breathlessness. Sputum production and recurrent chest infections were notable by their absence. The chest roentgenogram revealed a small cardiac silhouette along with the roentgenographical signs of advanced emphysema and lung hyperinflation. Arterial blood gases showed only mild hypoxaemia and hypercapnia and cor pulmonale was not a prominent clinical feature. A decrease in lung elastic recoil and a severely impaired diffusing capacity for carbon monoxide reflected the severe underlying emphysema.

The typical patient with predominant bronchitis was described as overweight, if not obese, with plethoric facies and obvious cyanosis. Chronic cough and sputum production were considered an essential feature of the bronchitic subtype. The other prominent aspects of the bronchitis patient were severe hypoxaemia, an accompanying hypercapnia, and consequent to the deranged blood gases, cor pulmonale and polycythaemia. Cor pulmonale was manifest clinically as peripheral oedema, cardiac enlargement and electrocardiographical signs of right ventricular enlargement. Reflecting the lack of severe emphysema, lung elastic recoil and diffusing capacity for carbon monoxide were normal or near normal.

The clinical features that distinguish COPD subtypes may be recognizable in selected patients, but most patients with COPD cannot be so simply categorized. It has been proposed that COPD represents a spectrum, with the emphysematous patients at one end and the bronchitic patients at the other. Because of extensive overlap between the two groups, clinical investigations have compared only those patients at the extreme ends of the spectrum. Subgroup distinctions have usually been made on clinical and physiological grounds, which have not been uniform.

Efforts to correlate lung pathology with the clinical subtype of COPD have generally been contradictory and inconclusive. Claims to the existence of the emphysematous and bronchitis subtypes of COPD rest largely on a single small study in which clinical data were compared with autopsy findings [43]. These findings could not be confirmed in subsequent similar studies by others [44,45]. Cor pulmonale is

generally considered an essential feature of the bronchitic patient but not the emphysematous patient. Consistent with this concept, small necropsy studies have shown little relationship between right ventricular weight and emphysema severity [46–48]. Similarly, the extent of emphysema as defined by CT imaging bears little relationship to the severity of blood gas or pulmonary haemodynamic abnormalities [49]. However, neither is there a strong relationship between mucous gland enlargement, long considered the essential lesion of the bronchitic subtype, and right ventricular weight [48,50,51]. Correlations of peripheral airways disease with right ventricular weight has been found by some investigators but not others [48,50].

Patients with COPD vary in their propensity for developing hypoxaemia, hypercapnia and pulmonary hypertension, so that the terms 'pink puffer' and 'blue bloater' may have some validity as clinical descriptive terms. However, very little is known as to why these differences exist. There is clearly no scientific justification for describing such patients as having either the emphysematous or bronchitic subtype of COPD.

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